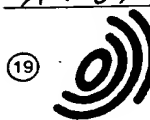


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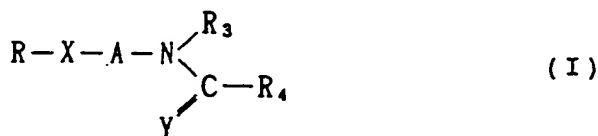
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(54) Pyridine derivatives, their production and use.

(57) There is disclosed a pharmaceutical composition for providing antiinflammatory, antipyretic, analgesic, antiallergic, immunosuppressing or immunomodulating activity which comprises a pyridine derivative of the formula (I) :



wherein R is an optionally substituted pyridine ring, X is a oxygen atom or -S(O)<sub>n</sub>-, wherein n is 0, 1 or 2, A is a bivalent C<sub>1-15</sub> hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom, R<sub>3</sub> is a hydrogen atom or an optionally substituted hydrocarbon residue, R<sub>4</sub> is an optionally substituted hydrocarbon residue or an optionally substituted monocyclic or bicyclic heterocyclic group, R<sub>3</sub> and R<sub>4</sub> may be joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form an optionally substituted heterocyclic group, or R<sub>3</sub> or R<sub>4</sub> may be independently attached to A to form a ring, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or diluent.

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FIELD OF THE INVENTION

The present invention relates to pyridine derivatives which are useful as a medicament, their production and use.

BACKGROUND OF THE INVENTION

Treatment of autoimmune diseases such as rheumatoid arthritis and the like has been carried out by symptomatic therapy in which inflammation is relieved by a non-steroidal antiinflammatory drug (NSAID). The NSAID's are classified into acidic antiinflammatory drugs and basic antiinflammatory drugs.

On the other hand, recently, more attention has been paid to causal therapy in which immunopathy is improved by immunomodulatory activity. Examples of drugs used for causal therapy include D-penicillamine, levamisole, lobenzarit and the like.

Most of these NSAID's are acidic antiinflammatory drugs represented by aspirin, indomethacin and the like. They have disadvantage of causing serious side effects such as a stomach ulcer and having difficulty in using them continuously for a long period for time. Further, although basic antiinflammatory drugs have strong analgesic activity they have weak antiinflammatory action and therefore they are unsuitable for chronic diseases.

Furthermore, immunomodulators are insufficient in their pharmacological effects, side effects, toxicity and the like. Thus, it is desired to develop better drugs which are suitable for both symptomatic and causal therapy.

Recently, adhesion protein [e.g., intercellular adhesion molecule (ICAM)] inhibitors which inhibit infiltration of inflammatory cells or block attachment of immunocytes which participate in antigen or cell recognition have been noted [Masayuki Miyasaka, Jikken-Igaku, 9, 289 (1991); D.L. Thiele and P.E. Lipsky, Immunology Today, 10, 375 (1989)]. There are possibilities that these drugs inhibit or mitigate inflammatory by a mechanism different from conventional one. Therefore, such drugs are expected to be antiinflammatory drugs, antiallergic drugs or immunosuppressants of new generation.

OBJECTS OF THE INVENTION

The main object of the present invention is to provide novel drugs which have immunomodulatory activity or adhesion protein expression inhibitory activity as well as improved antiinflammatory activity, antipyretic activity and analgesic activity.

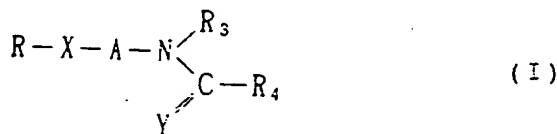
Compounds having a structure similar to that of the compounds in the present invention have been disclosed as starting materials for synthesis of cephems in EP-A-256542, JP-A 61-194794 and JP-A 62-148377. Further, N-[2-(4-pyridylthio)-ethyl]acetamide and N-[2-(4-pyridylsulfonyl)-ethyl]acetamide has been disclosed in Tr. Leninger. Khim.-Farmatseut. Inst., 1962 (16), 17-20 [Chem. Abstr. 61, 638g]. However, there is no disclosure of biological activities of these compounds.

SUMMARY OF THE INVENTION

The present inventors have synthesized and studied various pyridine derivatives having substituents. As a result, it has been found that a specific class of pyridine derivatives has excellent antiinflammatory activity, antipyretic activity, analgesic activity, immunomodulatory activity, antiallergic activity and adhesion protein expression inhibitory activity.

That is, according to the present invention, there are provided:

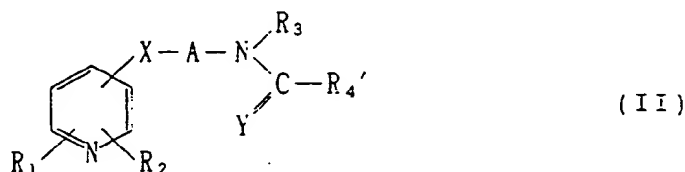
1) A pharmaceutical composition for providing antiinflammatory, antipyretic, analgesic, antiallergic, immunosuppressing or immunomodulating activity which comprises a pyridine derivative of the formula (I):



wherein R is an optionally substituted pyridine ring, X is a oxygen atom or -S(O)<sub>n</sub>-, wherein n is 0, 1 or 2, A is a bivalent C<sub>1-15</sub> hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom, R<sub>3</sub> is a hydrogen atom or an optionally substituted hydrocarbon residue, R<sub>4</sub> is an optionally

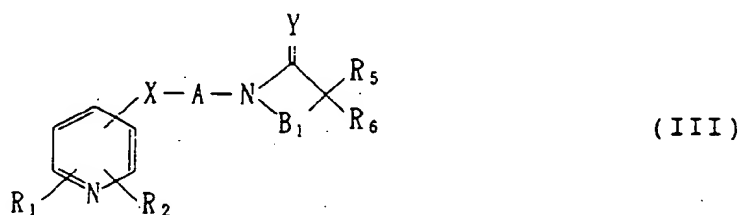
substituted hydrocarbon residue or an optionally substituted monocyclic or bicyclic heterocyclic group.  $R_3$  and  $R_4$  may be joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form an optionally substituted heterocyclic group, or  $R_3$  or  $R_4$  may be independently attached to A to form a ring, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or diluent;

2) A pyridine derivative of the formula (II):



wherein  $R_1$  and  $R_2$  are the same or different and are a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, hydroxy group, nitro group, cyano group, amino group, carbamoyl group, an acylamino group, a lower alkylamino group, a lower alkenylamino or an aralkylamino group; X is an oxygen atom or  $-S(O)_n-$ , wherein n is 0, 1 or 2, A is a bivalent  $C_{1-15}$  hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom,  $R_3$  is a hydrogen atom or an optionally substituted hydrocarbon residue,  $R_4'$  is (1) a  $C_{2-30}$  alkyl group, (2) a  $C_{2-30}$  alkenyl group, (3) a lower alkyl group substituted with a halogen atom, an aryl group or a heterocyclic group, (4) a lower alkenyl group substituted with a halogen atom or a heterocyclic group, (5) an optionally substituted aralkyl group, (6) an optionally substituted aryl group or (7) an optionally substituted monocyclic or bicyclic heterocyclic group, or a salt or solvate thereof;

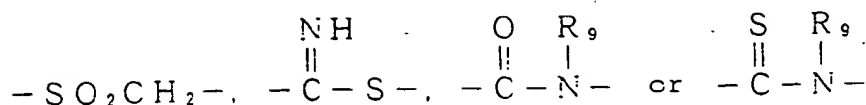
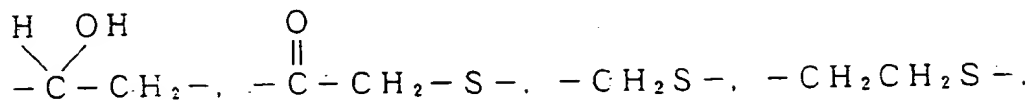
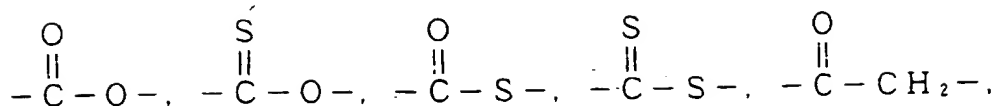
3) A pyridine derivative of the formula (III):



wherein  $R_1$  and  $R_2$  are the same or different and are a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, hydroxy group, nitro group, cyano group, amino group, carbamoyl group, an acylamino group, a lower alkylamino group, a lower alkenylamino group or an aralkylamino group, X is an oxygen atom or  $-S(O)_n-$ , wherein n is 0, 1 or 2; A is a bivalent  $C_{1-15}$  hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom,  $R_5$  and  $R_6$  are the same or different and are a hydrogen atom, a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl group or an optionally substituted aryl group, or  $R_5$  and  $R_6$  are joined to form a group of the formula:

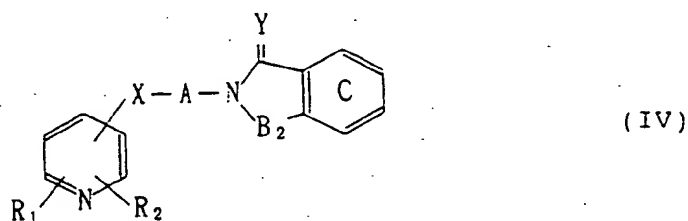


wherein  $R_7$  and  $R_8$  are the same or different and are a hydrogen atom, a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl group, an optionally substituted aryl group or an optionally substituted monocyclic or a bicyclic heterocyclic group, or  $R_7$  and  $R_8$  are linked together to form a ring,  $B_1$  is  $-(CH_2)_p-$ , wherein p is an integer of 1 to 4, or a group of the formula:



wherein  $\text{R}_9$  is a hydrogen atom, an optionally substituted lower alkyl, lower alkenyl or aralkyl group, or a salt or solvate thereof.

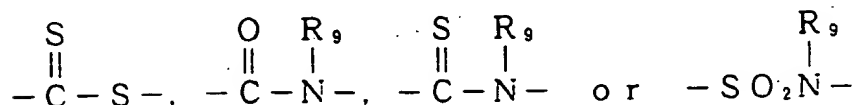
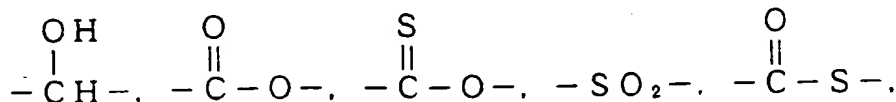
4) A pyridine derivative of the formula (IV):



wherein  $\text{R}_1$  and  $\text{R}_2$  are the same or different and are a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, hydroxy group, nitro group, cyano group, amino group, carbamoyl group, an acylamino group, a lower alkylamino group, a lower alkenylamino group or an aralkylamino group, X is an oxygen atom or  $-\text{S}(\text{O})_n-$ , wherein n is 0, 1 or 2, A is a bivalent  $\text{C}_{1-15}$  hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom, a group of the formula:

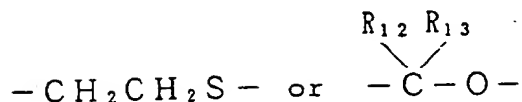
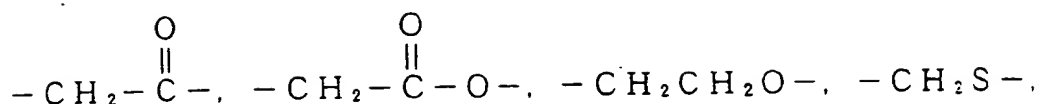


is an optionally substituted benzene ring,  $\text{B}_2$  is  $-(\text{CH}_2)_p-$ , wherein p is an integer of 1 to 4, or a group of the formula:

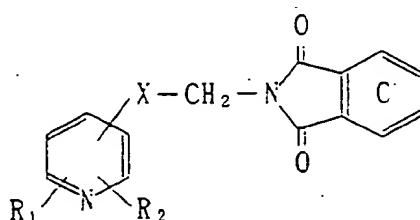


wherein  $\text{R}_9$  is a hydrogen atom, an optionally substituted lower alkyl, lower alkenyl or aralkyl group, or a group of the formula:





wherein  $\text{R}_{12}$  and  $\text{R}_{13}$  are the same or different and are a hydrogen atom, a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl group or an aryl group, or  $\text{R}_{12}$  and  $\text{R}_{13}$  may be linked together to form a ring, or a salt or solvate thereof, and 5) A pyridine derivative of the formula (V):



(V)

wherein  $\text{R}_1$  and  $\text{R}_2$  are the same or different and are a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, hydroxy group, nitro group, cyano group, amino group, carbamoyl group, an acylamino group, a lower alkylamino group, a lower alkenylamino group or an aralkylamino group, X is an oxygen atom or  $-\text{S}(\text{O})_n-$ , wherein n is 0, 1 or 2, a group of the formula:

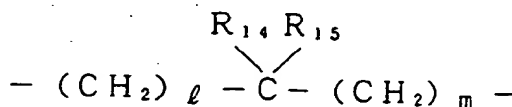


is an optionally substituted benzene ring, or a salt or solvate thereof.

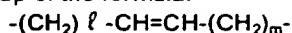
#### DETAILED DISCLOSURE OF THE INVENTION

In the formula (I), the optionally substituted pyridine ring represented by R may be substituted by the same or different 1 to 4, preferably 1 to 2 substituents such as a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, hydroxy group, nitro group, cyano group, amino group, carbamoyl group, an acylamino group, a lower alkylamino group, a lower alkenylamino group or an aralkylamino group.

Examples of the hydrocarbon residue represented by A in the above formula include a group of the formula:



wherein l and m each is 0 or an integer of 1 to 6,  $\text{R}_{14}$  and  $\text{R}_{15}$  are a hydrogen atom, a lower alkyl group, a lower alkenyl group, an optionally substituted aralkyl group or an optionally substituted aryl group, and  $\text{R}_{14}$  and  $\text{R}_{15}$  may be linked together with the adjacent carbon atom to form a 3 to 6 membered ring, and  $\text{R}_{14}$  or  $\text{R}_{15}$  may be linked to  $\text{R}_3$  or  $\text{R}_4$  to form a ring, or a group of the formula:



wherein l and m are as defined above.

Examples of the optionally substituted hydrocarbon residue of  $\text{R}_3$  and  $\text{R}_4$  include (1) a  $\text{C}_{2-30}$  alkyl group, (2) a  $\text{C}_{2-30}$  alkenyl group, (3) a lower alkyl group substituted with a halogen atom, an aryl group or a heterocyclic group, (4) a lower alkenyl group substituted with a halogen atom, an aryl group or a heterocyclic group, (5) an

optionally substituted aralkyl group and (6) an optionally substituted aryl group.

The monocyclic heterocyclic group represented by  $R_4$ ,  $R_7$  and  $R_8$  is a 5 to 6 membered monocyclic aromatic heterocyclic group or a saturated or unsaturated monocyclic non-aromatic heterocyclic group having 1 to 4 hetero atoms selected from the group consisting of oxygen, sulfur and nitrogen as its ring constituent atoms. Preferred examples thereof include thienyl (e.g., 2-thienyl, 3-thienyl, etc.), furyl (e.g., 2-furyl, 3-furyl, etc.), pyranyl, 2H-pyrrolyl, pyrrolyl (e.g., 2-pyrrolyl, 3-pyrrolyl, etc.), imidazolyl (e.g., 2-imidazolyl, 4-imidazolyl, etc.), pyrazolyl (e.g., 3-pyrazolyl, 4-pyrazolyl, etc.), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, etc.); isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, etc.), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, etc.), pyrazinyl, pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, etc.), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl, etc.) and the like. The above monocyclic heterocyclic group may be partially saturated. Examples of the partially saturated monocyclic heterocyclic group include pyrrolidinyl (e.g., 2-pyrrolidinyl, 3-pyrrolidinyl, etc.), pyrrolinyl (e.g., 2-pyrrolin-3-yl, etc.), imidazolinyl (2-imidazolin-4-yl, etc.), piperidyl (e.g., 2-piperidyl, 3-piperidyl, etc.), piperazinyl (e.g., 2-piperazinyl, etc.), morpholinyl (e.g., 3-morpholinyl, etc.) and the like.

The above monocyclic heterocyclic group represented by  $R_4$ ,  $R_7$  and  $R_8$  may have 1 to 4 substituents such as a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, nitro group, cyano group, hydroxy group, a lower alkoxy carbonyl group, carboxyl group, carbamoyl group, a lower alkyl carbamoyl group, a lower alkenyl carbamoyl group or the like.

The bicyclic heterocyclic group represented by  $R_4$ ,  $R_7$  and  $R_8$  is a condensed ring formed by a 5 to 6 membered aromatic heterocyclic group or a saturated or unsaturated non-aromatic heterocyclic group having 1 to 4 hetero atoms selected from the group consisting of oxygen, sulfur and nitrogen as ring constituent atoms. Preferred examples thereof include isobenzofuranyl (e.g., 1-benzofuranyl, etc.), chromenyl (e.g., 2H-chromen-3-yl, etc.), benzothienyl (e.g., 2-benzothienyl, etc.), indoliziny (e.g., 2-indoliziny, 3-indoliziny, etc.), isoindolyl (e.g., 1-isoindolyl, etc.), 3H-indolyl (e.g., 3H-indol-2-yl, etc.), indolyl (e.g., 2-indolyl, etc.), 1H-indazolyl (e.g., 1H-indazol-3-yl, etc.), purinyl (e.g., 8-purinyl, etc.), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, etc.), quinolyl (2-quinolyl, 3-quinolyl, etc.), phthalazinyl (e.g., 1-phthalazinyl, etc.), naphthylidinyl (e.g., 1,8-naphthylidin-2-yl, etc.), quinoxaliny (e.g., 2-quinoxaliny, etc.), quinazoliny (e.g., 2-quinazoliny, etc.), cinnoliny (e.g., 3-cinnoliny, etc.) and the like. The above bicyclic heterocyclic group may be partially saturated. Examples of the partially saturated bicyclic heterocyclic group include isochromanyl (e.g., 3-isochromanyl, etc.), indoliny (e.g., 2-indoliny, etc.), isoindoliny (e.g., 1-isoindoliny, etc.), 1,2,3,4-tetrahydro-2-quinolyl, 1,2,3,4-tetrahydro-3-isoquinolyl and the like.

The above bicyclic heterocyclic group represented by  $R_4$ ,  $R_7$  and  $R_8$  may have 1 to 4 substituents which are the same as those of the above monocyclic heterocyclic group represented by  $R_4$ ,  $R_7$  and  $R_8$ .

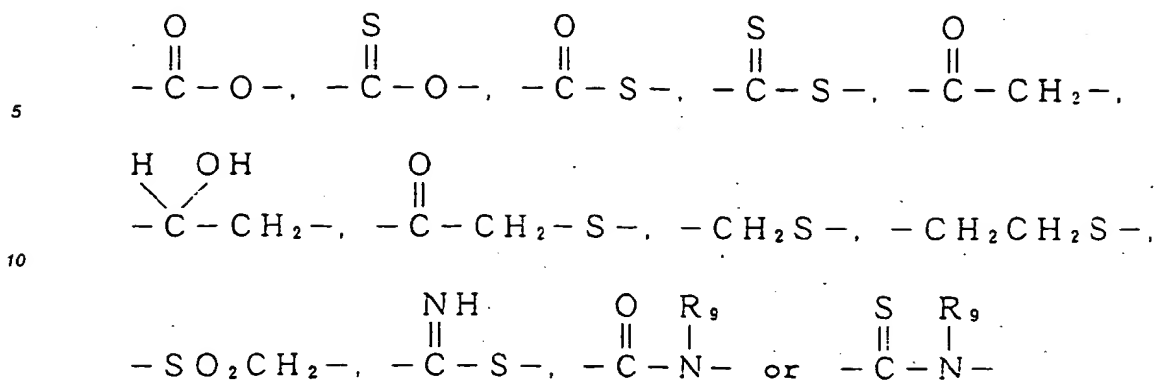
Examples of the heterocyclic group formed by  $R_3$  and  $R_4$  together with the carbamoyl group or the thiocarbamoyl group to which they are attached include a group of the formula (VI):



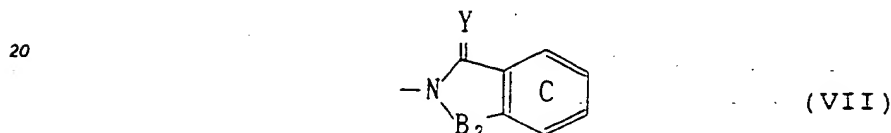
wherein Y is an oxygen or sulfur atom;  $R_5$  and  $R_6$  are the same or different and are a hydrogen atom, a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl group or an optionally substituted aryl group, or  $R_5$  and  $R_6$  are joined to form a group of the formula:



$R_7$  and  $R_8$  are the same or different and are a hydrogen atom, a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl group, an optionally substituted aryl group or an optionally substituted monocyclic or bicyclic heterocyclic group, or  $R_7$  and  $R_8$  are linked together to form a ring.  $B_1$  is  $-(CH_2)_p-$ , wherein p is an integer of 1 to 4, or a group of the formula:



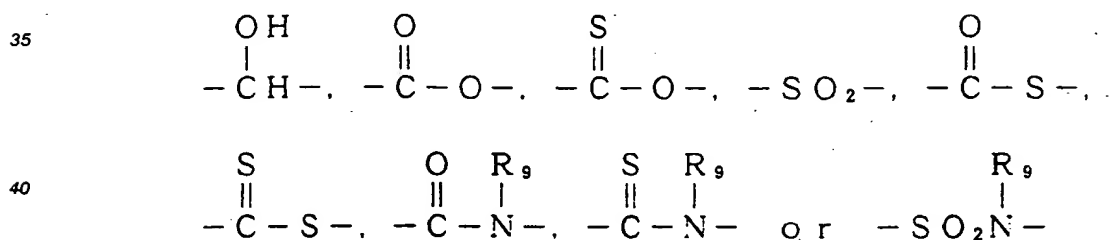
wherein  $\text{R}_9$  is a hydrogen atom, an optionally substituted lower alkyl, lower alkenyl or aralkyl group, or  $\text{B}_1$  is a group of the formula:



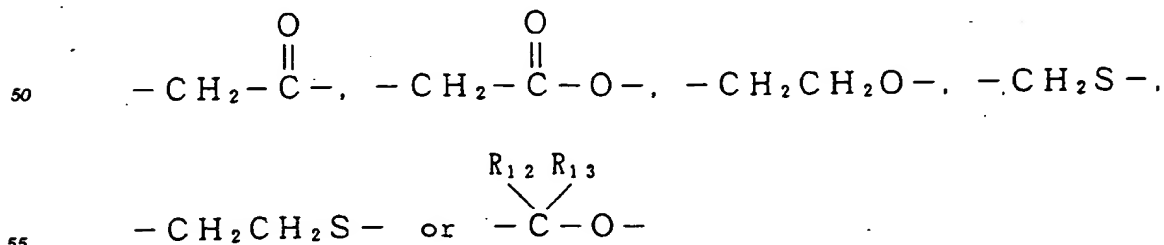
25 wherein Y is a oxygen or sulfur atom, a group of the formula



30 is an optionally substituted benzene ring,  $\text{B}_2$  is  $-(\text{CH}_2)_p-$ , wherein p is an integer of 1 to 4, or a group of the formula:



45 wherein  $\text{R}_9$  is a hydrogen atom, an optionally substituted lower alkyl, lower alkenyl or aralkyl group, or  $\text{B}_2$  is a group of the formula:



wherein  $\text{R}_{12}$  and  $\text{R}_{13}$  are the same or different and are a hydrogen atom, a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl or aryl

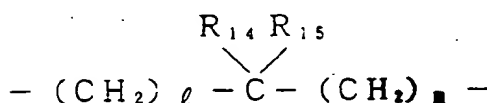
group, or  $R_{12}$  and  $R_{13}$  may be linked together to form a ring.

Examples of the substituent of the optionally substituted benzene ring of the formula:

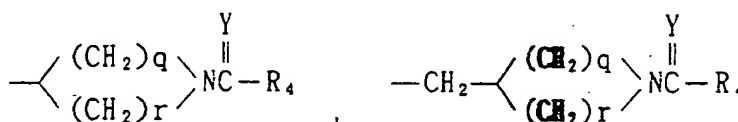


10 include a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl group or an aryl group, a halogen atom, nitro group, cyano group, a lower alkoxy group, amino group, a lower alkylamino group, a lower alkenylamino group, an acylamino group, acyl group, carbamoyl group and the like. The benzene ring may be substituted with 1 to 4, preferably 1 to 2 substituents which are the same or different.

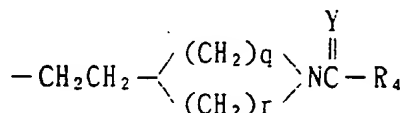
15 When  $R_3$  and  $R_4$  are independently attached to A to form a ring, A is a group of the formula:



wherein  $l$ ,  $m$ ,  $R_{14}$  and  $R_{15}$  are as defined above. Examples of a 3 to 6 membered ring formed by linkage between  $R_{14}$  and  $R_{15}$  included cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. Examples of the ring formed by linkage between  $R_{14}$  or  $R_{15}$  and  $R_3$  include groups of the formulas:

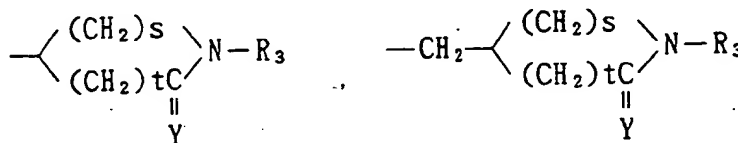


30 and

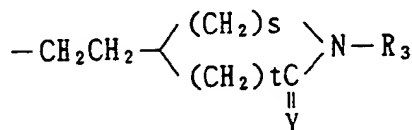


wherein  $q$  and  $r$  are 2 or 3, respectively and  $R_4$  and  $Y$  are as defined above.

40 Examples of the ring formed by linkage between  $R_{14}$  or  $R_{15}$  and  $R_4$  include groups of the formulas:



50 and



wherein  $s$  and  $t$  are 1 or 2, respectively and  $R_3$  and  $Y$  are as defined above.

Examples of the ring formed by linkage between  $R_7$  and  $R_8$  or between  $R_{12}$  and  $R_{13}$  include a monocyclic

hydrocarbon residue having 3 to 6 carbon atoms such as cyclopropyl, cyclobutyl, cycloheptyl, cyclohexyl and the like.

Examples of the "halogen atom" in each group of the above formulas include fluoro, bromo, chloro and iodo.

5        Examples of the "lower alkyl group" in each group of the above formulas include straight-chain or branched-chain alkyl groups having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl and the like.

Examples of the "lower alkenyl group" in each group of the above formulas include alkenyl groups having 2 to 6 carbon atoms such as vinyl, allyl, 2-butenyl, 3-butenyl and the like.

10       Examples of the substituent of the optionally substituted lower alkyl and lower alkenyl groups represented by  $R_3$  include a halogen atom, a lower alkoxy group, hydroxy group, a lower alkoxycarbonyl group, carboxyl group, carbamoyl group, a lower alkylcarbamoyl group, pyridylthio group and the like.

Examples of the "lower alkoxy group" in each group of the above formulas include straight-chain or branched-chain alkoxy groups having 1 to 6 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy and the like.

15       Examples of the "acylamino group" in each group of the above formulas include alkanoylamino groups and benzamide groups having 2 to 6 carbon atoms such as acetamido, propanoylamino, butyrylamino, pivaloylamino and the like.

20       Examples of the "lower alkylamino group" in each group of the above formulas include alkylamino groups whose alkyl moiety has 1 to 6 carbon atoms (e.g., methylamino, ethylamino, propylamino, butylamino, etc.), N,N-dialkylamino groups whose alkyl moieties have 1 to 6 carbon atoms, respectively (e.g., dimethylamino, diethylamino, dibutylamino, methylethylamino, etc.), groups wherein the alkyl moieties of the dialkyl moiety are joined to form a 5 or 6 membered ring structure (e.g., pyrrolidinyl, piperidino, etc.) and the like.

25       Examples of the "lower alkenylamino group" in each group of the above formulas include alkenylamino and N,N-dialkenylamino groups containing the "lower alkenyl groups" as exemplified above.

30       Examples of the "aralkylamino group" in each group in the above formulas include phenyl lower alkylamino groups whose alkyl moiety has 1 to 6 carbon atoms (e.g., benzylamino, phenethylamino, 3-phenylpropylamino, 4-phenylbutylamino, etc.), naphthyl lower alkylamino groups whose alkyl moiety has 1 to 6 carbon atoms [e.g., (1-naphthyl)methylamino, 2-(1-naphthyl)ethylamino, 2-(2-naphthyl)ethylamino, etc.], N,N-bis(phenyl lower alkyl)amino groups whose each alkyl moiety has 1 to 6 carbon atoms [e.g., dibenzylamino, diphenethylamino, bis(3-phenylpropyl)amino, etc.], N,N-bis(naphthyl lower alkyl)amino groups whose each alkyl moiety has 1 to 6 carbon atoms [e.g., bis[(1-naphthyl)methyl]amino, bis[(1-naphthyl)ethyl]amino, etc.] and the like.

35       The phenyl moiety of the phenyl lower alkylamino group and the N,N-bis(phenyl lower alkyl)amino group as well as the naphthyl moiety of the naphthyl lower alkylamino group and the N,N-bis(naphthyl lower alkyl)amino group may have 1 to 4 substituents such as a halogen atom, a lower alkyl group, a lower alkoxy group, a lower alkenyl group, a lower alkylcarbamoyl group, a lower alkenylcarbamoyl group and the like.

40       Examples of the "halogen atom", the "lower alkyl group" and the "lower alkoxy group" include the same groups as the "halogen atom", the "lower alkyl group", the "lower alkenyl group" and the "lower alkoxy group" in the groups of the above formulas, respectively.

Examples of the "lower alkenylcarbamoyl" group include N-alkenylcarbamoyl groups and N,N-dialkenylcarbamoyl groups containing the "lower alkenyl group" as exemplified above.

45       Examples of the lower alkoxycarbonyl group include alkoxycarbonyl groups having about 1 to 6 carbon atoms such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and the like. Examples of the lower alkylcarbamoyl group include N-alkylcarbamoyl groups whose alkyl moiety has 1 to 6 carbon atoms (e.g., methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, etc.), N,N-dialkylcarbamoyl groups whose each alkyl moiety has 1 to 6 carbon atoms (e.g., dimethylcarbamoyl, diethylcarbamoyl, dibutylcarbamoyl, methylethylcarbamoyl, etc.) and the like.

50       Examples of the "lower alkenylcarbamoyl" group include N-alkenylcarbamoyl groups and N,N-dialkenylcarbamoyl groups containing the "lower alkenyl group" as exemplified above.

55       Examples of the "optionally substituted aralkyl group" in each group of the above formulas include phenyl lower alkyl groups whose alkyl moiety has 1 to 6 carbon atoms (e.g., benzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, etc.), naphthyl lower alkyl whose each alkyl moiety has 1 to 6 carbon atoms [e.g., (1-naphthyl)methyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, etc.] and the like. The phenyl moiety of the phenyl lower alkyl group and the naphthyl moiety of the naphthyl lower alkyl group may have 1 to 4 substituents such as a halogen atom, a lower alkyl group, a lower alkenyl, a lower alkoxy group, nitro group, cyano group, hydroxy group, a lower alkoxycarbonyl group, carbamoyl group, a lower alkylcarbamoyl group, a lower alkenylcarbamoyl group or the like. Examples of the halogen atom include fluoro, bromo, chloro and iodo. Examples of the lower alkyl group

and the lower alkenyl groups include the same "lower alkyl group" and "lower alkenyl group" as exemplified above. Examples of the alkoxy group include straight-chain or branched-chain alkoxy groups having about 1 to 6 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy and the like. Examples of the lower alkoxycarbonyl group include alkoxycarbonyl groups having about 1 to 6 carbon atoms such as methoxy carbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and the like. Examples of the lower alkylcarbamoyl group include N-alkylcarbamoyl groups whose alkyl moiety has 1 to 6 carbon atoms (e.g., methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, etc.), N,N-dialkylcarbamoyl groups whose each alkyl moiety has 1 to 6 carbon atoms (e.g., dimethylcarbamoyl, diethylcarbamoyl, dibutylcarbamoyl, methylethylcarbamoyl, etc.) and the like.

Examples of the "optionally substituted aryl group" in each group of the above formulas include aromatic monocyclic or bicyclic hydrocarbon residues such as phenyl, 1-naphthyl, 2-naphthyl, phenanthryl and the like. The aryl group may have 1 to 4, preferably 1 or 2 substituents such as a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, nitro group, cyano group, oxo group, hydroxy group, amino group, an acylamino group, a lower alkoxycarbonyl group, carbamoyl group, a lower alkylcarbamoyl group, a lower alkenylcarbamoyl group or the like. Examples of the halogen atom include fluoro, bromo, chloro and iodo. Examples of the lower alkyl group include alkyl groups having 1 to 6 carbon atoms and examples of the lower alkenyl group include alkenyl groups having about 2 to 6 carbon atoms. As concrete examples of the alkyl group having 1 to 6 carbon atoms and the lower alkenyl group having 2 to 6 carbon atoms, there are such alkyl groups and alkenyl groups as exemplified above for the "lower alkyl group" and the "lower alkenyl group". Examples of the lower alkoxy group include alkoxy groups having 1 to 6 carbon atoms. Examples of the lower alkoxycarbonyl group include alkoxycarbonyl groups whose alkoxy moiety has 1 to 6 carbon atoms. Examples of the lower alkylcarbamoyl group include N-alkylcarbamoyl groups whose alkyl moiety has 1 to 6 carbon atoms and N,N-dialkylcarbamoyl groups whose each alkyl moiety has about 1 to 6 carbon atoms. As concrete examples of these groups, there are such groups as exemplified above for the lower alkoxy group, lower alkoxycarbonyl group and lower alkylcarbamoyl as the substituent of the phenyl moiety in the above aralkyl group. Examples of the "lower alkenylcarbamoyl group" include N-alkenylcarbamoyl groups and N,N-dialkenylcarbamoyl groups containing the "lower alkenyl group" as exemplified above. Examples of the aryl group having an oxo group include benzoquinonyl, naphthoquinonyl, anthraquinonyl and the like.

Examples of the "C<sub>2-30</sub> alkyl group" in the above each group include straight-chain or branched-chain alkyl groups having 2 to 30, preferably 2 to 10 carbon atoms (e.g., ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosanyl, heneicosanyl, docosanyl, tricosanyl, tetracosanyl, pentacosanyl, hexacosanyl, heptacosanyl, octacosanyl, nonacosanyl, triacontanyl, farnesyl, dihydrophytyl, etc.), cycloalkyl groups having 3 to 8 carbon atoms (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.), bicycloalkyl groups having 7 to 12 carbon atoms (e.g., norbornyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.0]octyl, etc.), tricycloalkyl groups having 7 to 12 carbon atoms (e.g., adamantyl, etc.), bicyclic hydrocarbon residues in which a condensed ring is formed by 5 to 8 membered rings (e.g., perhydropentalenyl, perhydroindenyl, perhydroazulenyl, perhydrocyclopenta-cyclooctenyl, perhydronaphthyl, perhydrobenzocycloheptenyl, perhydrobenzocyclooctenyl, perhydroheptalenyl, perhydrocycloheptacyclooctenyl, etc.), tricyclic hydrocarbon residues in which a condensed ring is formed by 5 to 8 membered rings [e.g., perhydroindacenyl (as,s), perhydro-acenaphthylenyl, perhydrophenanthryl, perhydroanthryl, etc.] and the like.

Examples of the C<sub>2-30</sub> alkenyl group in the above each group include alkenyl groups having 2 to 30 carbon atoms (e.g., vinyl, allyl, 9-octadecenyl, etc.), cycloalkenyl groups having 5 to 8 carbon atoms (e.g., cyclopentenyl, cyclohexenyl, etc.), bicycloalkenyl groups having 7 to 12 carbon atoms [e.g., bicyclo[2.2.2]oct-2-enyl, etc.], tricycloalkenyl groups having about 7 to 12 carbon atoms, bicyclic hydrocarbon residues in which a condensed ring is formed by a benzene ring and 5 to 8 membered ring [e.g., indanyl (e.g., 1-indanyl, 2-indanyl, etc.), indenyl (e.g., 1H-inden-1-yl, 1H-inden-2-yl, 1H-inden-3-yl, etc.), dihydronaphthyl (e.g., 1,2-dihydro-1-naphthyl, 1,2-dihydro-2-naphthyl, etc.), tetrahydronaphthyl (e.g., 5,6,7,8-tetrahydro-1-naphthyl, 5,6,7,8-tetrahydro-2-naphthyl, etc.), 5H-benzocycloheptenyl (e.g., 5H-5-benzocycloheptenyl, 5H-8-benzocycloheptenyl, etc.), dihydro-5H-benzocycloheptenyl (e.g., 6,7-dihydro-5H-8-benzocycloheptenyl, etc.), tetrahydrobenzocyclooctenyl (e.g., 5,6,7,8-tetrahydro-9-benzocyclooctenyl, etc.), etc.], tricyclic hydrocarbon residues in which a condensed ring is formed by two benzene rings and a 5 to 8 membered ring [e.g., acenaphthenyl (e.g., 1-acenaphthenyl, etc.), tetrahydroanthryl (e.g., 1,2,3,4-tetrahydro-1-anthryl, etc.), etc.] and the like.

As the "lower alkyl group substituted with a halogen atom, an aryl or a heterocyclic group", there are lower alkyl groups having 1 to 6 carbon atoms substituted with 1 to 3 halogen atoms, aryl groups and heterocyclic groups as exemplified above.

As the "lower alkenyl group substituted with a halogen atom, an aryl or a heterocyclic group", there are

lower alkenyl groups having 2 to 6 carbon atoms substituted with 1 to 3 halogen atoms, aryl groups and heterocyclic groups as exemplified above.

The compound (I) forms a salt such as an acid addition salt as well as a solvate. Examples of the acid to be used to form the acid addition salt of the compound (I) include inorganic acids (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, etc.) and organic acids (e.g., acetic acid, oxalic acid, methane-sulfonic acid, maleic acid, fumaric acid, citric acid, tartaric acid, lactic acid, etc.).

Examples of the solvent to be used to form the solvate include methanol, ethanol, propanol, isopropanol, acetone, tetrahydrofuran, dioxane and the like.

The compound of the formula (I) can have an asymmetric carbon atom. When two kinds of stereoisomers of R-configuration and S-configuration exist, each isomer and the mixture thereof are included in the scope of the present invention.

Among the compounds of the formula (I), the compounds of the formulas (II) to (V) are novel.

In the compound of the formula (II), preferably,  $R_1$  and  $R_2$  are the same or different and a hydrogen atom, amino group or an acylamino group. X is preferably an oxygen or sulfur atom. A is preferably a bivalent  $C_{1-6}$  hydrocarbon residue, more preferably, methylene, ethylene, propylene or butylene.  $R_3$  is preferably a hydrogen atom, an optionally substituted alkyl group or an optionally substituted aryl. Preferably,  $R_4$  is a  $C_{2-30}$  alkyl group, a halogenoalkyl group, an optionally substituted aryl or an optionally substituted monocyclic or bicyclic heterocyclic group. Y is preferably an oxygen atom.

In the compounds of the formula (III), preferably,  $R_1$  and  $R_2$  are the same or different and are a hydrogen atom, amino group or an acyl amino group. More preferably,  $R_1$  and  $R_2$  are each hydrogen atom. X is preferably an oxygen or sulfur atom. A is preferably a bivalent  $C_{1-6}$  hydrocarbon residue, more preferably, methylene, ethylene, propylene or butylene. Y is preferably an oxygen atom.  $R_5$  and  $R_6$  are the same or different and are a hydrogen atom or a lower alkyl group, or  $R_5$  and  $R_6$  are joined to form the group of the formula:



wherein  $R_7$  and  $R_8$  are the same and different and preferably are a hydrogen atom, a lower alkyl group, an optionally substituted alkyl group, an optionally substituted aryl or an optionally substituted monocyclic or bicyclic heterocyclic group.  $B_1$  is preferably  $-C(=O)-O-$ ,  $-C(=O)-S-$ ,  $-C(=O)-CH_2$  or  $-C(=O)-NR_9-$ , more preferably,  $-C(=O)-S-$  or  $-C(=O)-NR_9-$ , wherein  $R_9$  is as defined above.

In the compounds of the formula (IV), preferably,  $R_1$  and  $R_2$  are the same or different and are a hydrogen atom, amino group or an acylamino group. More preferably,  $R_1$  and  $R_2$  are each hydrogen atom. X is preferably an oxygen or sulfur atom. A is preferably a bivalent  $C_{1-6}$  hydrocarbon residue, more preferably, methylene, ethylene, propylene or butylene. Y is preferably an oxygen atom.  $B_2$  is preferably  $-(CH_2)_p-$ ,  $-(HO-)CH-$ ,  $-C(=O)-O-$ ,  $-C(=S)-O-$ ,  $-SO_2-$ ,  $-C(=O)-NR_9-$  or  $-C(=S)-NR_9-$ , more preferably  $-CH_2-$ ,  $-C(=O)-O-$ ,  $-C(=S)-O-$ ,  $-SO_2-$ ,  $-C(=O)-NR_9-$  or  $-C(=S)-NR_9-$ , wherein  $R_9$  is as defined above.  $R_9$  is preferably a hydrogen atom or an optionally substituted lower alkyl group. The substituent of the optionally substituted lower alkyl group is preferably pyridylthio group.

In the compounds of the formula (V), preferably,  $R_1$  and  $R_2$  are the same or different and are a hydrogen atom, amino group or an acylamino group. More preferably,  $R_1$  and  $R_2$  are each hydrogen atom. X is an oxygen or sulfur atom.

The specific examples of the pyridine derivative of the present invention are as follows:

- 4-[3-(N-Benzyl-N-trifluoroacetyl-amino)propylthio]pyridine hydrochloride,
- 4-[2-(Thianaphthene-2-carbonylamino)ethylthio]pyridine,
- 1,2-bis[N-[4-(4-Pyridylthio)butyl]-N-propionylamino]benzene dihydrochloride,
- 4-[4-(5-Benzylidene-2,4-thiazolidinedione)butylthio]pyridine,
- 4-[4-[5-(4-Chlorobenzylidene)-2,4-thiazolidinedione]butylthio]pyridine,
- 4-[4-[5-(2-Thienylmethylene)-2,4-thiazolidinedione]butylthio]pyridine,
- 4-[4-(5-Propylmethylene-2,4-thiazolidinedione)butylthio]pyridine,
- 4-(5,5-Dimethyloxazolidine-2,4-dione)methylthiopyridine,
- 4-[4-[5-(4-Pyridyl)methylene-2,4-thiazolidine dione]butylthio]pyridine,
- 4-[4-[5-(3-Pyridyl)methylene-2,4-thiazolidinedione]butylthio]pyridine,
- 4-[4-(5-Nonylmethylene-2,4-thiazolidinedione)butylthio]pyridine hydrochloride,
- 3-[3-(4-Pyridylthio)propyl]-2H-1,3-benzoxazine-2-thion-4(3H)-one,

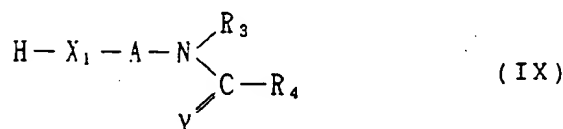
3-[4-(4-Pyridylthio)butyl]quinazoline-2,4-(1H,3H)-dione,  
 1,3-bis[4-(4-Pyridylthio)butyl]quinazoline-2,4-(1H,3H)-dione,  
 3-[4-(4-Pyridylthio)butyl]-2H-1,3-benzoxazine-2-thion-4(3H)-one,  
 4-Saccharinmethylthiopyridine,  
 4-Saccharinmethylthiopyridine hydrochloride,  
 1,3-bis[4-(2-Pyridylthio)butyl]quinazoline-2,4(1H,3H)-dione,  
 1-(4-Pyridylthio)methyl-3-[4-(4-pyridylthio)butyl]quinazoline-2,4(1H,3H)-dione dihydrochloride,  
 1,3-bis[4-(4-Pyridylthio)butyl]quinazoline-2(1H)-thion-4(3H)-one dihydrochloride,  
 4-(Phthalimidomethylthio)pyridine, and  
 4-(Phthalimidomethyloxy)pyridine.

The pyridine derivative of the present invention can be synthesized, for example, according to the following processes.

(A) When X is O or S in the formula (I), a compound of the formula (VIII):



wherein E is halogen such as chloro, bromo or iodo, and R is as defined above, is reacted with a compound of the formula (IX)

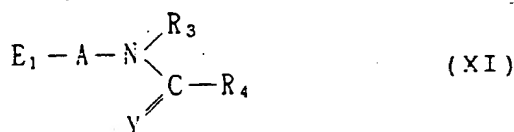


wherein  $\text{X}_1$  is O or S, and the other groups are as defined above.

(B) When X is O or S in the formula (I), a compound of the formula (X):



wherein each symbol is as defined above, is reacted with a compound of the formula (XI):



wherein  $\text{E}_1$  is halogen such as chloro, bromo, iodo or the like or a leaving group such as methanesulfonyloxy, p-toluenesulfonyloxy or the like, and the other symbols are as defined above.

(C) A compound of the formula (XII):



wherein each symbol is as defined above, is reacted with a compound of the formula (XIII):

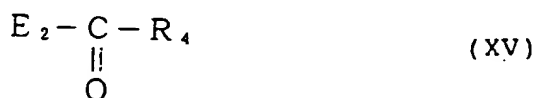


wherein each symbol is as defined above.

(D) When Y is O in the formula (I), a compound of the formula (XIV):



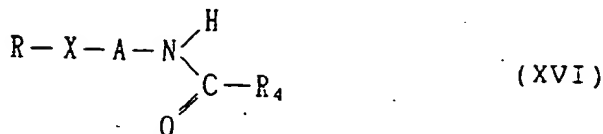
wherein each symbol is as defined above, is reacted with a compound of the formula (XV):



wherein  $\text{E}_2$  is halogen such as chloro, bromo or the like,  $\text{O-C(=O)-R}_4$  or OH, and the other symbol is as defined above.



(E) When Y is O and R<sub>3</sub> is an alkyl group or aralkyl group in the formula (I), a compound of the formula (XVI):



wherein each symbol is as defined above, is reacted with the compound of the formula (XVII):

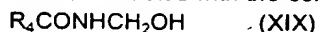


wherein R<sub>3</sub>' is an alkyl group or aralkyl group, and the other group is as defined above.

(F) When X is S and A is CH<sub>2</sub> in the formula (I), a compound of the formula (XVIII):

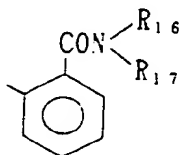


wherein each symbol is as defined above, is reacted with the compound of the formula (XIX):

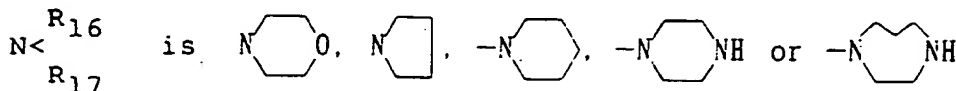


wherein each symbol is as defined above.

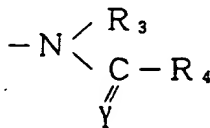
(G) When, in the formula (I), R<sub>3</sub> is H, Y is O, R<sub>4</sub> is a group of the formula:



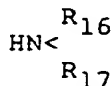
wherein R<sub>16</sub> and R<sub>17</sub> are the same or different and are a hydrogen atom or a lower alkyl group, or may be joined to form a ring, and the group of the formula:



the compound of the formula (I) wherein the group of the formula:

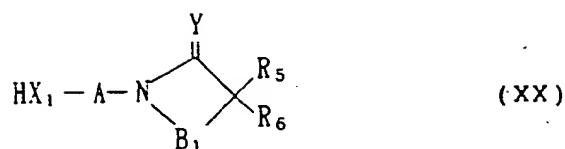


is phthalimido group, is reacted with a compound of the formula:



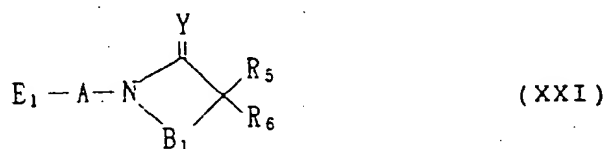
(H) When, in the formula (I), X is S(O), S(O)<sub>2</sub>, the compound of the formula (I) wherein X is S is reacted with an oxidizing agent.

(I) When, in the formula (I), R<sub>3</sub> and R<sub>4</sub> are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VI), the compound of the formula (VIII) is reacted with a compound of the formula (XX):



wherein each symbol is as defined above.

(J) When, in the formula (I),  $\text{R}_3$  and  $\text{R}_4$  are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VI), the compound of the formula (X) is reacted with a compound of the formula (XXI):



wherein each symbol is as defined above.

(K) When, in the formula (I),  $\text{R}_3$  and  $\text{R}_4$  are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VI), the compound of the formula (XII) is reacted with a compound of the formula (XXII):

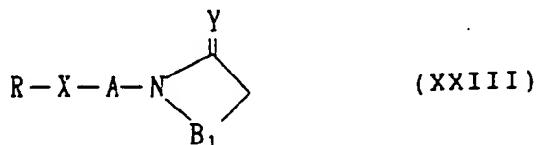


wherein each symbol is as defined above.

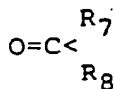
(L) When, in the formula (I),  $\text{R}_3$  and  $\text{R}_4$  are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VI) and  $\text{R}_5$  and  $\text{R}_6$  are joined to form the group of the formula:



a compound of the formula (XXIII):

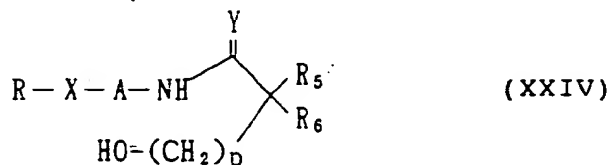


wherein each symbol is as defined above, is reacted with a compound of the formula:



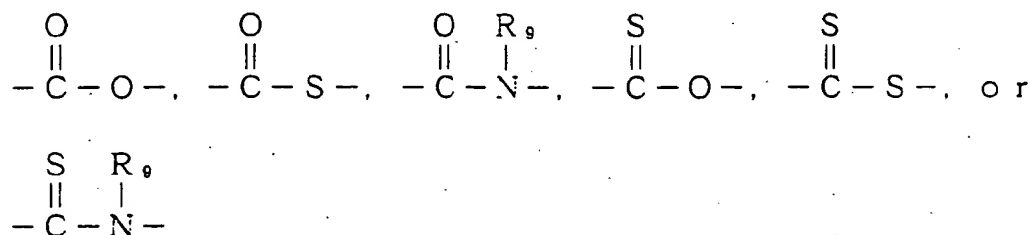
wherein each symbol is as defined above.

(M) When, in the formula (I),  $R_3$  and  $R_4$  are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VI) and  $B_1$  is  $-(CH_2)_p-$ , a compound of the formula (XXIV):

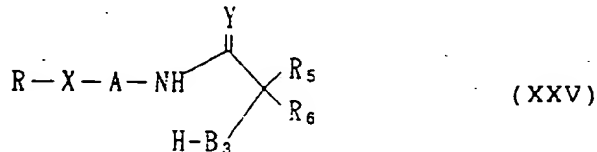


wherein each group is as defined above, is subjected to cyclodehydration.

(N) When, in the formula (I),  $R_3$  and  $R_4$  are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VI) and  $B_1$  is represented by the formula:



a compound of the formula (XXV):

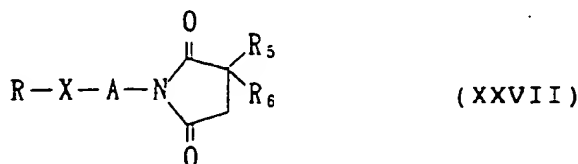


wherein  $B_3$  is O, S or  $-\text{N}(\text{R}_9)-$ , and the other groups are as defined above, is reacted with the compound of the formula (XXVI):



wherein  $E_3$  is an imidazolyl group, chloro or phenoxy group and the other group is as defined above.

(O) When, in the formula (I),  $R_3$  and  $R_4$  are joined together with the carbamoyl group or thiocarbamoyl group to which they are attached to form the group of the formula (VI) and Y is O and  $B_1$  is  $-\text{CH}(\text{OH})-\text{CH}_2-$ , a compound of the formula (XXVII):

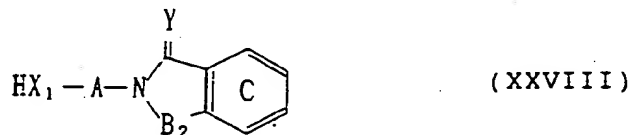


wherein each symbol is as defined above, is reduced with a reducing agent, e.g., sodium borohydride.

(P) When, in the formula (I),  $R_3$  and  $R_4$  are joined together with the carbamoyl group or thiocarbamoyl group to which they are attached to form the group of the formula (VI) and X is S(O) or S(O)<sub>2</sub>, the compound (I)

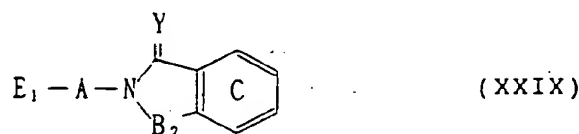
whose X is S is reacted with an oxidizing agent.

(Q) When, in the formula (I),  $R_3$  and  $R_4$  are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VII), the compound of the formula (VIII) is reacted with a compound of the formula (XXVIII):



wherein each symbol is as defined above.

(R) When, in the formula (I),  $R_3$  and  $R_4$  are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VII), the compound of the formula (X) is reacted with a compound of the formula (XXIX):



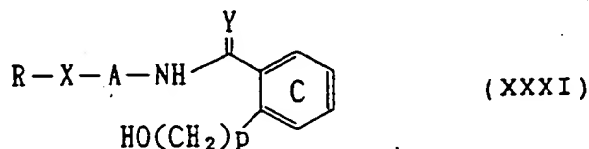
wherein each symbol is as defined above.

(S) When, in the formula (I),  $R_3$  and  $R_4$  are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VII), the compound of the formula (XII) is reacted with a compound of the formula (XXX):



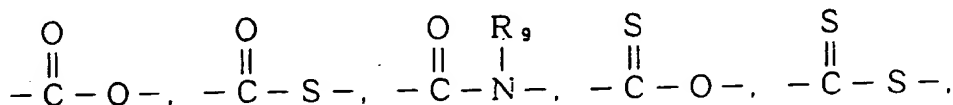
wherein each symbol is as defined above.

(T) When, in the formula (I),  $R_3$  and  $R_4$  are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VII) and  $B_2$  is  $-(\text{CH}_2)_p$ , a compound of the formula (XXXI):

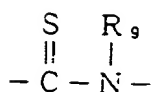


is cyclized by dehydration.

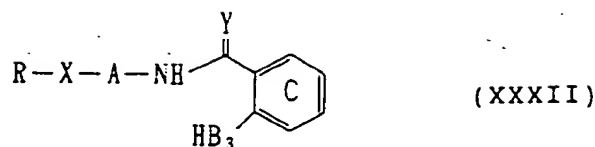
(U) When, in the formula (I),  $R_3$  and  $R_4$  are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VII) and  $B_2$  is a group of the formula:



or

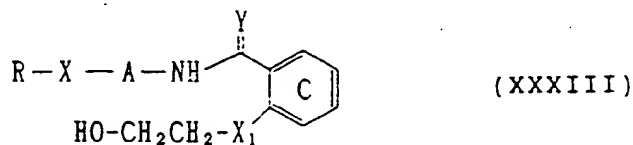


a compound of the formula (XXXII):



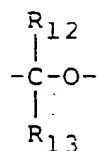
wherein each symbol is as defined above, is reacted with the compound of the formula (XXVI).

(V) When, in the formula (I),  $\text{R}_3$  and  $\text{R}_4$  are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VII) and  $\text{B}_2$  is  $-\text{CH}_2\text{CH}_2\text{X}_1-$ , a compound of the formula (XXXIII):

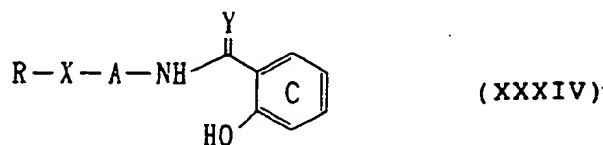


wherein each symbol is as defined above, is subjected to cyclodehydration.

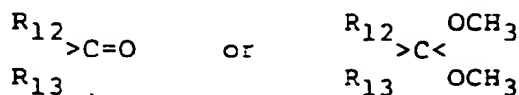
(W) When, in the formula (I),  $\text{R}_3$  and  $\text{R}_4$  are joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form the group of the formula (VII) and  $\text{B}_2$  is a group of the formula:



a compound of the formula (XXXIV):



wherein each symbol is as defined above, is reacted with a compound of the formula:

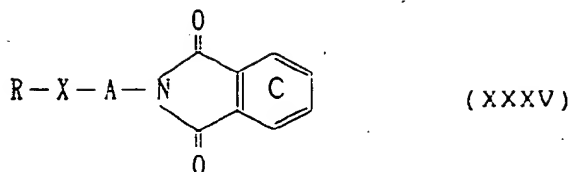


wherein each symbol is as defined above.

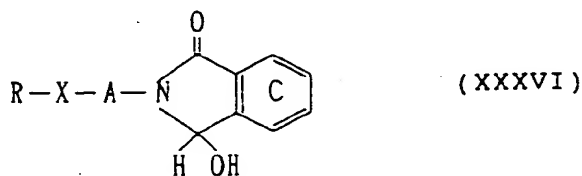
(X) When, in the formula (I),  $\text{R}_3$  and  $\text{R}_4$  are joined together with the carbamoyl group to which these are bonded to form the group of the formula (VII) and  $\text{Y}$  is  $\text{O}$  and  $\text{B}_1$  is



a compound of the formula (XXXV):



wherein each symbol is as defined above, is reduced with a reducing agent, e.g., sodium borohydride. (Y) When, in the formula (I),  $\text{R}_3$  and  $\text{R}_4$  are joined together with the carbamoyl group to which they are attached to form the group of the formula (VII) and Y is O and B<sub>1</sub> is  $\text{CH}_2$ , a compound of the formula (XXXVI):



wherein each symbol is as defined above, is reduced with a reducing agent, e.g., sodium borohydride in a solvent, e.g., trifluoroacetic acid.

(Z) When, in the formula (I),  $\text{R}_3$  and  $\text{R}_4$  are joined together with the carbamoyl group to which they are attached to form the group of the formula (VII) and X is  $\text{S(O)}$  or  $\text{S(O)}_2$ , the compound (I) whose X is S is reacted with an oxidizing agent.

In the reaction of the compound (VIII) with the compound (IX) in the above process A, the compound (IX) is used in an amount of 1 equivalent to large excess based on the compound (VIII). The reaction can be carried out at  $-20$  to  $+200^\circ\text{C}$  in a solvent in the presence of a basic compound such as sodium hydroxide, potassium hydroxide, sodium hydride, potassium carbonate, triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene or the like. Examples of the solvent to be used in the reaction include water, lower alcohols (e.g., methanol, ethanol, propanol, etc.), ketones (e.g., acetone, methyl ethyl ketone, etc.), ethers (e.g., tetrahydrofuran, etc.), aprotic polar solvents (e.g., N,N-dimethylformamide, dimethylsulfoxide, etc.) and the like.

The reaction of the compound (X) with the compound (XI) in the process B is carried out under the same conditions as those in the reaction of the compound (VIII) with the compound (IX) in the process A.

The reaction of the compound (XII) with the compound (XIII) in the process C is carried out under the same conditions as those in the reaction of the compound (VIII) with the compound (IX) in the process A.

In the reaction of the compound (XIV) with the compound (XV) whose  $\text{E}_2$  is chloro, bromo or  $-\text{C(=O)R}_4$  in the process D, the compound (XV) is used in an amount of 1 equivalent to large excess based on the compound (XIV). The reaction can be carried out at  $-30$  to  $+200^\circ\text{C}$  in a solvent in the presence or absence of an inorganic base (e.g., potassium carbonate, sodium bicarbonate, etc.) or an organic base [e.g., triethylamine, pyridine, dimethylaniline, 1,4-diazabicyclo[2.2.2]octane (DABCO)]. As the solvent to be used in the reaction, there are, for example, halogenated hydrocarbons (e.g., methylene chloride, chloroform, dichloroethane, etc.), ethers (e.g., diethyl ether, tetrahydrofuran, dimethoxyethane, etc.), esters (e.g., methyl acetate, ethyl acetate, etc.), aprotic polar solvents (e.g., N,N-dimethylformamide, dimethyl sulfoxide, etc.) and the like.

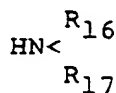
The reaction of the compound (XIV) with the compound (XV) whose  $\text{E}_2$  is OH in the process D is carried out by using the compound (XV) in an amount of 1 to 3 equivalents based on the compound (XIV) under conventional conditions for peptide syntheses. For example, the reaction is carried out in a solvent at  $-30$  to  $+100^\circ\text{C}$  by using N,N-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diethyl cyanophosphonate, 1,1'-carbonyldiimidazole or the like as a condensation agent. As the solvent to be used in the reaction, there are, for example, ketones (e.g., acetone, methyl ethyl ketone, etc.), ethers (e.g., tetrahydrofuran, etc.), halogenated hydrocarbons (e.g., methylene chloride, chloroform, etc.), aprotic polar solvents (e.g.,

N,N-dimethylformamide, etc.) and the like.

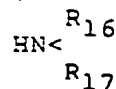
The reaction of the compound (XVI) with the compound (XVII) in the process E is carried out under the same conditions as those in the reaction of the compound (VIII) with the compound (IX) in the process A.

The reaction of the compound (XVIII) with the compound (XIX) in the process F is carried out at -30 to +100°C in a solvent or without using any solvent in the presence of trifluoroacetic acid by using the compound (XIX) in an amount of 1 equivalent to large excess based on the compound (XVIII). As the solvent to be used in the reaction, there are, for example, methylene chloride, chloroform, dichloroethane and the like.

The reaction of the compound (I) with the compound of the formula:



wherein each symbol is as defined above, in the process G is carried out at -30 to +100°C in a solvent. The amount of the compound of the formula:



wherein each symbol is as defined above, is 1 equivalent to large excess relative to the compound (I). As the solvent to be used in the reaction, there are, for example, water, lower alcohols (e.g., methanol, ethanol, propanol, etc.), ethers (e.g., tetrahydrofuran, etc.), halogenated hydrocarbons (e.g., methylene chloride, chloroform, dichloroethane, etc.) and the like.

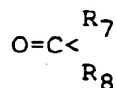
The oxidation of the compound (I) whose X is S in the process H is carried out at -30 to +100°C in the presence of a solvent by using an oxidizing agent in an amount of 1 equivalent to large excess based on the compound (I) whose X is S. As the solvent to be used in the reaction, there are, for example, water, methanol, ethanol, dichloromethane, chloroform and the like. Examples of the oxidizing agent include m-chloroperbenzoic acid, sodium metaperiodate, hydrogen peroxide and the like.

The reaction of the compound (VIII) with the compound (XX) in the process I is carried out under the same conditions as those in the reaction of the compound (VIII) with the compound (IX) in the process A.

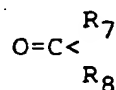
The reaction of the compound (X) with the compound (XXI) in the process J is carried out under the same conditions as those in the reaction of the compound (VIII) with the compound (IX) in the process A.

The reaction of the compound (XII) with the compound (XXII) in the process K is carried out under the same conditions as those in the reaction of the compound (VIII) with the compound (IX) in the process A.

The reaction of the compound (XXIII) with the compound of the formula:



wherein each symbol is as defined above, is carried out at -30 to +200°C in a solvent in the presence of an inorganic base (e.g., potassium bicarbonate, sodium bicarbonate, etc.), an organic base (e.g., piperidine, pyrrolidine, etc.) or sodium acetate. The amount of the compound of the formula:



wherein each symbol is as defined above, is 1 equivalent to large excess relative to the compound (XXIII). As the solvent to be used in the reaction, there are, for example, water, lower alcohols (e.g., methanol, ethanol, propanol, etc.), ketones (e.g., acetone, methyl ethyl ketone, etc.), aprotic polar solvents (e.g., N,N-dimethylformamide, dimethyl sulfoxide, etc.), acetic acid, propionic acid and the like.

The cyclization by dehydration of the compound (XXIV) in the process M can be carried out at -80 to +100°C

in a solvent in the presence of a dehydrating agent. As the dehydrating agent to be used in the reaction, there are, for example, methanesulfonyl chloride or p-toluenesulfonyl chloride in combination with a base. Examples of the base include triethylamine, pyridine, diisopropyl ethyl amine and the like. As the solvent to be used in the reaction, there are, for example, ketones (e.g., acetone, methyl ethyl ketone, etc.), ethers (e.g., tetrahydrofuran, etc.), halogenated hydrocarbons (methylene chloride, chloroform, dichloroethane, etc.), aprotic polar solvents (e.g., N,N-dimethylformamide, dimethyl sulfoxide, etc.) and the like.

The reaction of the compound (XXV) with the compound (XXVI) in the process N is carried out at -30 to +100°C in a solvent. The amount of the compound (XXVI) is 1 to 3 equivalents relative to the compound (XXV). As the solvent to be used in the reaction, there are, for example, halogenated hydrocarbons (e.g., methylene chloride, chloroform, dichloroethane, etc.), ethers (e.g., diethyl ether, tetrahydrofuran, etc.), N,N-dimethylformamide and the like.

The reduction of the compound (XXVII) in the process O is carried out at -30 to +100°C in a solvent. The amount of sodium borohydride is 1 equivalent to large excess relative to the compound (XXVII). As the solvent to be used in the reaction, there are, for example, water, methanol, ethanol and the like.

The oxidation of the compound (I) in the process P is carried out under the same conditions as those in the process H.

The reaction of the compound (VIII) with the compound (XXVIII) in the process Q is carried out under the same conditions as those in the reaction of the compound (VIII) with the compound (IX) in the process A.

The reaction of the compound (X) with the compound (XXIX) in the process R is carried out under the same conditions as those in the reaction of the compound (VIII) with the compound (IX) in the process A.

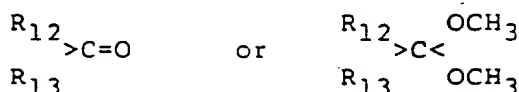
The reaction of the compound (XII) with the compound (XXX) in the process S is carried out under the same conditions as those in the reaction of the compound (VIII) with the compound (IX) in the process A.

The cyclization by dehydration of the compound (XXXI) in the process T is carried out under the same conditions as those in the reaction of the compound (XXIV) in the process M.

The reaction of the compound (XXXII) with the compound (XXVI) in the process U is carried out under the same conditions as those in the reaction of the compound (XXV) with the compound (XXVI) in the process N.

The cyclization by dehydration of the compound (XXXIII) in the process V is carried out under the same conditions as those in the reaction of the compound (XXIV) in the process M.

The reaction of the compound (XXXIV) with the compound of the formula:



wherein each symbol is as defined above, in the process W is carried out under conventional conditions of acetanol syntheses. The reaction is carried out, for example, at -30 to +150°C in an solvent in the presence of an acid. As the acid to be used in the reaction, there are, for example,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in which Et means ethyl, p-toluenesulfonic acid, camphorsulfonic acid and the like. Examples of the solvent include benzene, toluene, xylene, N,N-dimethylformamide and the like.

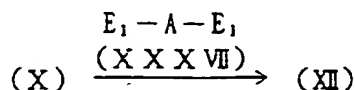
The reduction of the compound (XXXV) in the process X is carried out under the same conditions as those in the reduction of the compound (XXVII) with sodium borohydride in the process O.

The reduction of the compound (XXXVI) in the process Y is carried out at -10 to +100°C in trifluoroacetic acid by using a reducing agent, e.g., sodium borohydride in an amount of 1 equivalent to large excess.

Oxidation of the compound (I) in the process Z is carried out under the same conditions as those in the process H.

The starting compounds for the production of the compounds (I) according to the invention can be produced by a known method or a per se known method, for example, in the following manner:

The compound (XII), when X is O or S, can be obtained, for example, according to the following process:

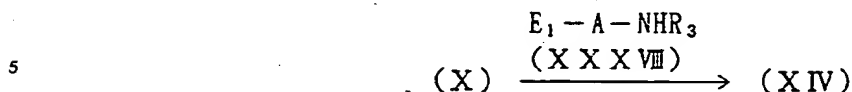


wherein each symbol is as defined above.

The reaction of the compound (X) with the compound (XXXVII) is carried out under the same conditions as those in the reaction of the compound (VIII) with the compound (IX) in the process A.



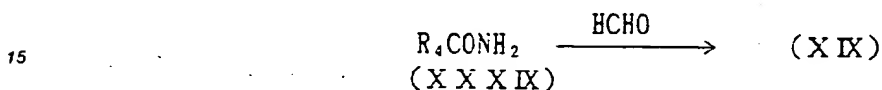
The compound (XIV), when X is O or S, can be obtained, for example, according to the following process:



wherein each symbol is as defined above.

The reaction of the compound (X) with the compound (XXXVIII) is carried out under the same conditions as those in the reaction of the compound (VIII) with the compound (IX) in the process A.

The compound (XIX) can be obtained, for example, according to the following process:



wherein each symbol is as defined above.

The reaction of the compound (XXXIX) with formaldehyde is carried out at 0 to +200°C in a solvent in the presence or absence of a base by using formaldehyde in an amount of 1 equivalent to large excess based on the compound (XXXIX). As the base to be used in the reaction, there are, for example, potassium carbonate, potassium hydroxide, sodium hydroxide and the like. Examples of the solvent include water, methanol, ethanol, N,N-dimethylformamide and the like.

The compound (I) can be separated and purified from the reaction mixture according to conventional separation and purification techniques such as extraction, concentration, filtration, recrystallization, column chromatography, thin layer chromatography or the like.

The compound (I) of the present invention and a pharmaceutically acceptable salt or solvate thereof have cyclooxygenase inhibitory activity, 5-lipoxygenase inhibitory activity, antiinflammatory activity, antipyretic activity, analgesic activity, antiallergic activity, immunomodulatory activity and adhesion protein expression inhibitory activity. Examples of the adhesion proteins include ICAM-1, ICAM-2, ELAM-1 (endothelial leukocyte adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1) which participate infiltration of inflammatory cells and antigen or cell recognition among by immunocytes as well as LFA-1 (lymphocyte function-associated antigen-1), Mac-1 (macrophage antigen-1) and the like. Therefore, these compounds are useful as an analgesic, antipyretic or antiinflammatory agent for acute and chronic inflammatory diseases (e.g., rheumatism, osteoarthritis, etc.), an immunotherapeutic agent (immunosuppressive agent and immunomodulator) against autoimmune diseases (e.g., rheumatism, etc.) and cancer, an antiallergic agent, an antiasthmatic agent, 5-lipoxygenase inhibitory agent. Further, they are useful as agents for treating thrombotic diseases (cardiac infarction, arterial embolism, venous embolism, etc.), nephritis, fulminant hepatitis, implantation immunorejection and the like.

When the compound (I) or a pharmaceutically acceptable salt or solvate thereof is used as the above medicament, the compound (I) or a pharmaceutically acceptable salt or solvate thereof is mixed with an appropriate pharmaceutically acceptable carriers, excipients, diluents (e.g., starch, physiological saline, etc.) and the like, and can be administered orally or parenterally in the per se known form such as powders, granules, tablets, capsules, injection preparations or the like. The dosage is varied depending upon a particular administration route, conditions of a disease to be treated, age or weight of a patient to be treated and the like. However, for example, in the case of treatment of, e.g., thrombotic diseases by oral administration to an adult patient, it is preferred that the dosage is 0.2 to 50 mg/kg/day, preferably 0.5 to 30 mg/kg/day and can be administered 1 to several times daily.

The following Experiments, Examples and Reference Examples further illustrate the present invention in detail but are not to be construed to limit the scope thereof.

#### Experiment 1

##### Cyclooxygenase Inhibitory Activity

##### [Test Method]

A rat (Jcl:wistar, male, 12 to 15 weeks old) was subjected to peritoneotomy under anesthesia, and 8 ml of

blood was taken from the abdominal aorta using a syringe [in which 0.72 ml of 3.2 % sodium citrate was pre-sucked]. The blood was centrifuged at room temperature (for 15 seconds at 2000 rpm and for 5 seconds at 3000 rpm, and thereafter centrifugation was stopped without using a brake), platelet-rich plasma (PRP) was taken, and the remaining blood was further centrifuged (at 3000 rpm for 10 minutes) to obtain platelet-poor plasma (PPP). The number of platelets in PPP was counted and PRP was diluted with PPP to adjust the concentration of platelets to  $10^6/\mu\text{l}$ . Arachidonic acid (25  $\mu\text{l}$ , 500  $\mu\text{g}/100 \mu\text{l}$ ) and 2.5  $\mu\text{l}$  of a test compound were added to 0.225 ml of this PRP, and was allowed to stand at 37°C for 15 minutes. Then, 1.1 ml of ethanol was added thereto and the mixture was shaken well, and centrifuged (at 2000 rpm, for 10 minutes). Water (1 ml) was added to 1 ml of the supernatant and the mixture was injected into a high performance liquid chromatography column (HPLC), and chromatographed under the following conditions to measure the peak height of 12 (S)-hydroxy-5,8,10-hepta-decatrienoic acid (HHT). As a control, the measurement was carried out according to the same manner except for using 2.5  $\mu\text{l}$  of the solvent used for dissolving the test compound in place of the test compound.

The inhibitory percentage at respective concentrations was calculated using the following equation to obtain  $\text{IC}_{50}$ .

The inhibitory percentage (%) =  $(1 - \text{As}/\text{Ac}) \times 100$  wherein As is the peak height of HHT in the test compound and Ac is the peak height of HHT in the control.

#### [Results]

The results are shown in Table 1.

Table 1

#### Cyclooxygenase inhibitory activity

Compound (Example No.)	$\text{IC}_{50}$ ( $\mu\text{M}$ )
Indomethacin	14.0
(control compound)	
1	1.6
7	4.4
8	1.1
9	2.2
10	2.2

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	14	13.2
	15	5.1
5	16	12.9
	17	1.5
	18	7.0
10	25	3.4
	26	3.5
15	27	5.4
	28	5.6
	30	6.6
20	31	4.6
	32	6.5
25	33	2.8
	34	2.9
	35	2.3
30	36	6.0
	39	4.4
35	40	7.6
	41	11.3
	42	13.1
40	43	13.0
	44	3.3
	45	6.6
45	46	7.9
	51	8.9
50	53	8.6
55		

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	54	9.0
	55	8.7
5	57	3.6
	58	7.9
	59	3.5
10	60	4.2
	61	11
15	73	2.8
	76	13
	78	5.2
20	81	6.8
	83	10
25	84	4.5
	85	1.4
	88	1.2
30	90	4.9
	93	6.3
35	96	13
	99	12
	100	8.0
40	101	3.2
	104	7.7
	105	5.1
45	106	3.7
	107	4.3
50	109	6.2
55		

	110	11.0
	111	7.0
5	112	13.0
	119	4.6
10	122	3.8
	123	3.3
	124	5.5
15	129	2.5
	146	5.1
	147	1.8
20	148	3.1
	154	6.0
25	156	2.9
	166	12
	168	3.6

30

Experiment 2

## 5-Lipoxygenase Inhibitory Activity

## 35 [Test Method]

A solution of a given concentration of a test compound (0.01 ml) was added to 0.9 ml of a rat basophilic leukemia cell suspension [ $10^7$  cells/mast cell medium (150 mM NaCl/3.7 mM KCl/3.0 mM  $\text{Na}_2\text{HPO}_4$ /3.5 mM  $\text{KH}_2\text{PO}_4$ /0.9 mM  $\text{CaCl}_2$ /5.6 mM dextrose, adjusted to pH 7.0 with 30 % NaOH)] and the mixture was allowed to stand at 37°C for 5 minutes. Then, 0.1 ml of mast cell medium containing 50  $\mu\text{g}$  of arachidonic acid and 1  $\mu\text{g}$  of calcium ionophore (A-23187) were added and the mixture was allowed to stand at 37°C for 15 minutes. Ethanol (1 ml) was added thereto and the mixture was shaken well, and filtered (Membrane filter, 0.45  $\mu\text{m}$ ). A part of the filtrate was injected into a HPLC column, and chromatographed under the following conditions to measure the peak height of 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene  $\text{B}_4$  ( $\text{LTB}_4$ ). As a control, the measurement was carried out according to the same manner except that 0.01 ml of the solvent used for dissolving the test compound was used in place of the test compound.

The inhibitory percentage (%) was calculated from the following equation to obtain  $\text{IC}_{50}$ .

The inhibitory percentage (%) =  $(1 - \text{As}/\text{Ac}) \times 100$  wherein As is the peak height of 5-HETE or  $\text{LTB}_4$  of the test compound and Ac is the peak height of 5-HETE or  $\text{LTB}_4$  of a control.

50

## [Results]

The results are shown in Table 2.

55

Table 2

## 5-Lipoxygenase inhibitory activity

	Compound (Example No.)	5-HETE	LTB <sub>4</sub>
		IC <sub>50</sub> (μM)	IC <sub>50</sub> (μM)
5			
10	1	16.8	16.1
	3	22.2	17.5
15	4	17.4	11.8
	17	17.5	14.3
	21	21.5	16.4
20	77	3.5	3.2
	94	2.4	2.0
25	95	0.044	0.033
	109	1.4	1.2
	128	6.1	5.4
30	133	4.6	4.3
	149	2.3	2.2
35	150	2.6	2.5
	151	1.8	1.1
	153	1.3	0.79
40	155	3.8	3.7

Experiment 3

## 45 In vitro ART (antigen-responding T-cell) Proliferation Test

## [Test Method]

50 A male Lewis rat (7 weeks old) was sensitized with 250 μg/rat of killed *M. tuberculosis* H 37 RA to induce adjuvant arthritis, and the inguen lymph node was removed after 14 days. This was suspended in a RPMI-1640 culture medium containing 5 % fetal calf serum (FCS) to obtain a single cell suspension and incubated at 37°C for 1 hour in a nylon wool column. The column was eluted with the same culture medium, and cells which did not adhere to the column were used as T cells.

55 On the other hand, spleen cells were prepared as antigen-presenting cell from a nonsensitized male Lewis rat (8 to 9 weeks old) and the cells were used after irradiation of 2500 R soft X-rays.

The above T cells (5 x 10<sup>5</sup> cells/well) and spleen cells (1 x 10<sup>5</sup> cells/well) were incubated in RPMI-1640 culture medium (total volume 200 μl) containing 2% of syngeneic rat serum (treated at 56°C for 30 minutes) together with purified protein derivative (PPD) (final concentration 2 μg/ml) in 0.5 % CO<sub>2</sub> at 37°C for 72 hours.

After addition of  $^3\text{H}$ -Tdr (0.5  $\mu\text{Ci}/\text{well}$ ), the mixture was further incubated for 24 hours and cells were recovered to measure the radioactivity of Tdr which was taken in.

A solution of a test compound (20  $\mu\text{l}$ ) was added just before the addition of PPD and it was present throughout the incubation period. The effect of the test compound was indicated as an inhibitory percentage relative to the amount of  $^3\text{H}$ -Tdr which was taken in T cells by PPD:

[Results]

The results are shown in Table 3.

Table 3

In vitro ART proliferation test

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	Compound (Example No.)	% Inhibition of ART growth	
		Concentration of compound	
		1 $\mu$ M	10 $\mu$ M
	24	29	35*
15	25	44**	-7
	32	43**	37**
	33	33	46**
20	34	31**	47**
	35	18	33**
25	73	23	82***
	74	-3	52**
	75	5	45**
30	76	3	38**
	77	28	85**
	90	34	49*
35	91	44*	42*
	93	42*	11
40	94	33*	70*
	95	20	32*
	97	30	31*
45	100	19	32*
	101	39*	12
50	105	-4	-49**

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	109	-11	-33*
	110	-21*	1
5	111	30**	-12
	115	18	53**
	116	10	31**
10	117	3	39**
	118	8	38*
15	119	13	43*
	120	16	74**
	123	15	66**
20	140	-9	-25**
	141	-21*	64**
25	145	17	-42**
	146	22	20*
	147	9	72***
30	149	-10	19*
	150	-31	75***
	151	-1	74***
35	152	-20	68***
	153	-20	75***
40	154	16*	27*
	155	4	78***
	157	-50	62**
45	160	-14	33*
	162	-31	-54*
50	163	-227***	99*
55			

164	3	-54*
171	96*	41

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\*:p<0.05 ; \*\*:p<0.01 ; \*\*\*:p<0.001

10 Experiment 4

## Rat Carrageenin Pedal Edema Inhibitory Activity

## [Test Method]

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A Jcl: SD male rat (6 weeks old, weight 160-220 g) was used. After the measurement of the volume of dexter hind limb foot pad, a test compound suspended in 5% gum arabic solution was administered orally. Immediately after the administration, water was further administered orally so that the total administration volume of liquid became 5 ml/rat. After one hour, 0.05 ml of 1% carrageenin suspension in physiological saline was injected subcutaneously in the foot pad to induce edema [Winter, C. A., Risley, E. A. and Nuss, G. W.: Proc. Soc. exp. Biol. Med. 111, 544 (1962)]. Three hours after injection of carrageenin, the volume of dexter limb was measured, and the edema volume was calculated by the difference between the volume after injection and the volume of pre-injection.

## 25 [Results]

The results are shown in Table 4.

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Table 4

Rat carrageenin pedal edema inhibitory activity

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	Compound (Example No.)	Dose (mg/kg)	Inhibitory percentage (%)
10	28	50	25*
	29	50	25*
15	31	50	32*
	33	50	37*
	42	50	34**
20	43	50	24*
	46	50	39**
25	47	50	25*
	54	50	45*
	55	50	41**
30	57	50	35*
	58	50	48**
35	59	50	35*
	62	50	36*
		12.5	20*
40	63	50	34**
	65	50	39**
	68	50	23*
45	90	50	21*
	97	50	29*
50	100	50	22*

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	101	50	26*
	104	50	21*
5	105	50	31*
	109	50	25*
10	110	50	44**
	112	50	42**
	113	50	35
15	114	50	28*
	116	50	45**
	118	50	31**
20	124	50	51**
	126	50	30**
25	127	50	32**
	129	50	34*
	132	50	45**
30	133	50	27*
	136	50	33*
	138	50	25*
35	141	50	36**
	143	50	27**
40	145	50	22*
	156	50	32*
	159	50	25*
45	162	50	34*
	163	50	29*
50	169	50	44**

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172	50	19**
173	50	23*

\*:  $p < 0.05$  ; \*\*:  $p < 0.01$

# Experiment 5

## Mouse Phenylquinone Writhing Inhibitory Activity

### [Test Method]

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A Slc: ICR male mouse (4 weeks, weight 17 to 24 g) was used. A test compound suspended in 5% gum arabic solution was administered orally. After 30 minutes, 0.1 ml/10 g body weight of 0.02% phenylquinone solution in water (dissolved by the aid of 5% ethanol) was injected intraperitoneally, and writhing and stretching responses of individual animals were measured for 20 minutes [Siegmund, E., Cadmus, R. and Lu, G.; Proc. Soc. exp. Biol. Med. 95, 729 (1957)].

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### [Results]

The results are shown in Table 5.

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### Table 5

#### Mouse phenylquinone writhing inhibitory activity

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Compound (Example No.)	Dose (mg/kg)	Inhibitory percentage (%)
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1	100	61**
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	23	50	58*
	24	50	56**
5	25	50	60**
	26	50	67**
	32	50	63**
10	35	50	60***
	40	50	45**
15	41	50	73**
	42	50	51*
	43	50	48*
20	46	50	66***
	47	50	47*
25	48	50	31*
	51	50	72***
	54	50	58**
30	55	50	58**
	57	50	71**
35	58	50	34*
	59	50	49**
	60	50	41**
40	62	50	55**
	63	50	56**
	64	50	56**
45	65	50	80***
	67	50	49*
50	68	50	50*

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	71	50	55*
	73	50	75***
5	74	50	51*
	75	50	54**
	76	50	61**
10	77	50	62**
	78	50	55***
15	79	50	48**
	81	50	75**
	82	50	47**
20	83	50	59**
	84	50	84**
25	85	50	70***
	86	50	51*
	87	50	47*
30	88	50	41*
	89	50	62*
35	90	50	53**
	91	50	52**
	92	50	74**
40	93	50	41**
	101	50	66***
	105	50	59***
45	109	50	89***
	111	50	64***

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\*:p<0.05 ; \*\*:p<0.01 ; \*\*\*:p<0.001

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Experiment 6

## Mouse Acetic Acid Writhing Inhibitory Activity

## 5 [Test Method]

Ten male Slc: ICR mice, 4 weeks old, per 1 group were used. A test compound was administered orally, and after 30 minutes, 0.1 ml/10 g body weight of physiological saline containing 0.6% acetic acid was injected intraperitoneally. For 20 minutes, writhing (in agony condition) response by administration of acetic acid was counted regarding individual animals. The inhibitory percentage relative to the mean response counts of a control group was calculated regarding respective animals in a test compound administration group. The test compound was suspended in 5% gum arabic solution, and the administration volume was 0.2 ml/10 g.

## [Results]

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The results are shown in Table 6.

Table 6

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Mouse acetic acid writhing inhibitory activity

25	Compound	Dose (mg/kg)	Inhibitory percentage (%)
	(Example No.)		
	124	50	69**
30	147	50	46*
	150	50	54**
35	153	50	49*
	167	50	62*
	169	50	96***
40	170	50	91***
	173	50	75***
	176	50	87***
45	179	50	66***

50 \*:p<0.05 ; \*\*:p<0.01 ; \*\*\*:p<0.001

Experiment 7

## Pain Relief Test By Randall Celit Method

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Seven to eight male Jcl: Winter rats, 5 weeks old, per one group were used. 0.1 ml of 10% brewer's yeast physiological saline suspension was injected subcutaneously in the rat dexter hind limb foot pad to induce inflammation. After three hours, the pain threshold was measured by pressure stimulating pain relief measuring



apparatus manufactured by Ugo Basile Company (Cat. No. 7200) using an index of false pain reflex in the inflammatory limb (dexter hind limb), and this was taken as response threshold value in the inflammatory limb. A test compound was administered after additional 45 minutes orally, and the threshold was measured after one and two hours. The efficacy was determined by comparing threshold of a control group and that of the test compound group. The test compound was suspended in 5% gum arabic solution and the administration volume was 0.5 ml/100 g.

[Results]

The results are shown in Table 7.

Table 7

Randall Celit method

		% Of control	
Compound	Dose	1 hour	2 hours
(Example No.)	(mg/kg)		
169	200	242±21.9***	326.1±80.1*
	50	215.2±16.1	158.4±26.2
173	200	222.7±26.4***	165.8±24.9*

\*:p<0.05 ; \*\*\*:p<0.001

Experiment 8

Antipyretic Activity

Six male DS line rats, 7 weeks old, weighing 200 to 240 g (Nihon Clea) per one group were used. According to the method of Winder et al. (J. Pharmac. Exp. Ther. 138: 405 (1963)), a suspension of 15% brewer's yeast (Sigma) in physiological saline (1 ml/100 g, b.w.) was injected subcutaneously at 16 hours before measurement of the body temperature to induce pyrexia. After injection of yeast, only water was provided, and each rat was bred separately in a five duplicate cage. At 16, 17 and 18 hours after yeast injection, the rectal temperature was measured by a thermistor thermometer (Takara Kogyo K.K.), and this was taken as the basal body temperature. The rectal temperature was indicated by the temperature which was digitally displayed at 15 seconds after a thermistor thermometer sensor was inserted in the rectum to the extent of 4 cm. Animals having the body temperature of not lower than 38.5°C at 18 hours after yeast injection were selected, and a test compound was administered orally (1 ml/100 g, b.w.). As a control, only the solvent was provided. Upon administration, the body temperature of the control group and that of the test compound-administered group were adjusted to the same temperature. The rectal temperature was measured every hour till five hours after administration.

[Results]

The results are shown in Table 8.

Table 8

## Antipyretic activity

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	Compound	Dose	$\Delta^{\circ}\text{C}$ (peak time)
	(Example No.)	(mg/kg)	
10	24	50	-1.33** (2h)
	32	50	-1.39** (1h)

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	40	50	-2.00**(3h)
	42	50	-0.80**(1h)
5	46	50	-4.08**(4h)
	54	50	-3.50**(5h)
	57	50	-1.28**(4h)
10	62	50	-1.40**(4h)
	64	50	-2.58**(3h)
15	65	50	-0.62* (4h)
	71	50	-0.52* (2h)
	73	50	-0.65* (2h)
20	83	50	-0.82**(2h)
	84	50	-0.97**(3h)
25	85	50	-1.00**(2h)
	89	50	-2.72**(3h)
	111	50	-0.68**(2h)
30	112	50	-1.58**(3h)
	113	50	-0.82* (4h)
35	114	50	-1.14* (4h)
	116	50	-0.63* (3h)
	124	50	-1.52**(2h)
40	126	50	-1.21**(2h)
	141	50	-2.40**(3h)
		12.5	-1.60**(3h)
45	169	50	-2.43**(2h)
		12.5	-2.13**(2h)
50	173	50	-2.02**(2h)

55 \*:p<0.05, \*\*:p<0.01

Experiment 9

## Rat Reversed Passive Arthus Reaction (skin) Inhibitory Activity

5 This reaction was induced by using domestic rabbit anti-egg albumin (EA) antiserum according to the method of Chang and Otterness [Chang, Y. -H. and Otterness, I. G.: Eur. J. Pharmacol. 69, 155 (1981)]. Using six Jcl: SD male rats (7 weeks old, weight about 250 g) per one group, the hair was removed in the back under ether anesthesia, 1 ml of 0.5% EA physiological saline was injected intracutaneously from the tail vein, and further each 0.1 ml of diluted antiserum (6 mg protein antibody/ml) was injected in the back on both dexter and sinister sides. A test compound (50 mg/kg) was suspended in 5% gum arabic solution and the suspension was administered orally at one hour before EA administration. Acceleration of permeability through the vessel by the reaction was measured by injecting 1 ml of 1 % Evans blue physiological saline intravenously at three hours after the induction of the reaction. Then, after 30 minutes, the rat was sacrificed by exsanguination. The skin was peeled off and the area of pigment spot (length x breadth, mm<sup>2</sup>) was measured.

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## [Results]

The results are shown in Table 9.

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Table 9

Rat reversed passive Arthus reaction inhibitory

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activity

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Compound (Example No.)	Inhibitory percentage (%)
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24	46**
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25	24**
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32	41**
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35	30**
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40

41	35**
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53	21*
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56	32*
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62	27*
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\*:p&lt;0.05,      \*\*:p&lt;0.01

Experiment 10

## Activity To Rat Adjuvant Arthritis

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## [Test Method]

A male SD rat or Lewis rat (6 weeks old, weight 190-230 g, Nihon Clea) was sensitized by intracutaneously

injecting 0.05 ml of Freund's complete adjuvant (liquid paraffin suspension of 0.5% killed *M. tuberculosis*) in dexter hind limb foot pad. The volume of dexter hind limb was measured just before the adjuvant sensitization and the 14th day after sensitization. A test compound was suspended in 5% gum arabic solution and it was administered through the entire period from the day 0 to the day 13.

[Results]

The results are shown in Table 10.

Table 10

Adjuvant arthritis test

Compound (Example No.)	Dose (mg/kg)	Swelling inhibitory percentage (%)
73	50	52**

\*\* :  $p < 0.01$

Experiment 11

Adhesion Protein Expression Inhibitory Activity

[Test Method]

The various concentrations of test compounds were added to the human umbilical cord-derived vascular endothelial cells [sold by Klabo] which were seeded in the gelatin coat plate and the mixture were incubated at 37 °C for 15 minutes. Then, the human tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ; sold by Genzyme] was added therein to the final concentration of 1 ng/ml and incubation was carried out at 37 °C for 3 hours for expression of ELAM-1 and for 6 hours for that of ICAM-1. After the reaction, the cells were fixed using glutaraldehyde and the expression amount of ELAM-1 and ICAM-1 was measured by the cell-ELISA method. That is, the expression was determined by fluorescence-labeling the adhesion proteins on the cells in the system using anti-ELAM-1 antibody BBA-2 and anti-ICAM-1 antibody BBA4 as the first antibody as well as horseradish peroxidase-labeled rabbit anti-mouse IgG antibody as the second antibody.

[Results]

The results are shown in Table 11.

Table 11

## Adhesion protein expression inhibition test

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10	Compound	Concentration	Expression Inhibitory	
	(Example No.)	( $\mu$ M)	Potency (%)	
			ELAM-1	ICAM-1
	73	30	-	42
15	123	30	-	34
	141	3	-	21
		30	-	54
20	146	13	33	-
	147	13	96	83
25	150	30	-	94
	151	30	-	60
30	157	30	-	78
	171	13	94	75
	172	13	31	34
35	173	30	-	35
	180	13	29	35
40	184	10	47	-
	185	10	33	-
	187	10	53	79
45	198	13	-	25
	200	13	71	83

50 Experiment 12

## Effect On Acute Renal Failure Induced By Renal Ischemia-Reperfusion

55 Male Sprague-Dawley rats (6 to 7 weeks old) were anesthetized using pentobarbital sodium (50 mg/kg, i.p.) and bilateral renal arteries were completely occluded for 45 minutes followed by reperfusion. After 20 hours of the reperfusion, the blood was collected from the abdominal aorta under anesthesia and the blood urea nitrogen (BUN) was determined. The test compounds were orally (5 ml/kg) administered 1 hour before the ligation of the renal arteries.

## [Results]

The results are shown in Table 12.

Table 12

The effects on acute renal failure induced by the renal ischemia followed by reperfusion in rats

Compound (Exmample No.)	Dose (mg/kg)	Blood urea nitrogen (mg/dl)
vehicle		106±5
73	50	68±3
vehicle		100±10
150	50	76.8±16.9
157	50	62.4±7.0
vehicle		93±11
171	50	64±11

As shown in Table 12, these invented compounds inhibited the increase in BUN in the model of acute renal failure induced by occlusion of the bilateral renal arteries of rats followed by reperfusion.

Experiment 13

PAF Induced Respiratory Tract Constriction Inhibitory Activity

[Test Method]

Male and female Hartley guinea pigs, weighing about 400 g, were used. The guinea pigs were fixed at dorsal position under urethane anesthesia (1.5 g/kg, i.p.). One leg of cannula (having four legs) was inserted in the trachea and two of three other legs were bound to the respirator (Harvard apparatus rodent respirator). The remaining one leg (side branch) was bound to the bronchospasm transducer 7.020 (Ugobasile). Under the conditions of 5 to 7 ml of air supply/time, 70 times/min. of supply time and 10 cm H<sub>2</sub>O of pulmonary pressure load, the amount of over flow air was recorded on Rectigraph (Rectigraph-8S, Saneissoki) via the transducer. After Gallamine triethoxide treatment (1 mg/kg, i.v.), PAF was administered intravenously (1.0 µg/kg) and the maximum respiratory tract constriction response was observed after 30 seconds. Under these conditions, the inhibitory activity of the test compounds were examined. The test compounds were suspended in 5% gum arabic solution, respectively, and they were administered intravenously 2 minutes before PAF administration

[Results]

The results are shown in Table 13.

Table 13

PAF induced respiratory tract constriction  
inhibitory test

Compound (Example No.)	Dose (mg/kg)	Inhibitory activity (%)
141	3	51.7**
147	3	50.7
162	3	39.8
199	3	53.5**
200	10	61.4**
203	0.3	90.4**

\*\* :  $p < 0.01$

#### Example 1

Synthesis of 4-[3-(caprylamino)propylthio]pyridine

i) Synthesis of 4-(3-aminopropylthio)pyridine dihydrochloride

4-Mercaptopyridine (50.0 g, 0.44 mol) was dissolved in 2N aqueous solution of sodium hydroxide (500 ml, 1.00 mol) and 98.4 g (0.44 mol) of 3-bromopropylamine hydrobromide was added and the mixture was heated at 60°C for 2 hours. After cooling, the reaction mixture was extracted with ethyl acetate. The extract was separated and dried, and the solvent was distilled off to obtain 67.0 g of a free base (90.5%, yellow oil).

The free base (57.0 g, 0.34 mol) was treated with 2N hydrogen chloride solution in methanol (350 ml, 0.70 mol) and the solvent was distilled off. The resulting crystals were washed with acetone and dried to obtain 82.0 g of the desired compound (quant., colorless powder), mp: 150.0-152.0°C.

Anal. for  $C_{10}H_{14}N_2OS \cdot 0.5H_2O$ ,

Calcd.: C; 38.41, H; 6.04, N; 11.20

Found: C; 38.48, H; 6.10, N; 11.11

NMR (200MHz,  $D_2O$ )  $\delta$ : 2.18 (2H, quint., J=7Hz), 3.22 (2H, t, J=7Hz), 3.37 (2H, t, J=7Hz), 7.83 (2H, dd, J=7, 2Hz), 8.45 (2H, d, J=7Hz)

IR (KBr)  $cm^{-1}$ : 3370, 3320, 1620

ii) Synthesis of 4-[3-(caprylamino)propylthio]pyridine

To a solution of 2.50 g (10.4 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 4.77 ml (34.2 mmol) of triethylamine in 200 ml of methylene chloride was added 2.37 ml (11.4 mmol) of capryl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain the powder which was washed with ether and dried to obtain 2.80 g of the desired compound (83.9%, colorless powder), mp: 64.0-65.0°C.



Anal. for  $C_{18}H_{30}N_2OS$ .

Calcd.: C; 67.04, H; 9.38, N; 8.69

Found: C; 67.09, H; 9.55, N; 8.59

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.86 (3H, t, J=7Hz), 1.24 (12H, m), 1.61 (2H, quint., J=7Hz), 1.92 (2H, quint., J=7Hz), 2.16 (2H, t, J=7Hz), 2.99 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz), 5.80 (1H, m), 7.08 (2H, dd, J=5, 2Hz), 8.37 (2H, dd, J=5, 2Hz)

IR (KBr)  $cm^{-1}$ : 3300, 3070, 1640

## Example 2

### Synthesis of 3-[3-(caprylamino)propylthio]pyridine

A solution of 1.00 g (5.49 mmol) of 3-(dimethylaminocarbonylthio)pyridine in 1 ml of methanol was added to 2N aqueous solution of sodium hydroxide (20 ml, 50.0 mmol) and the mixture was heated with stirring for 30 minutes. After cooling, 1.20 g (5.49 mmol) of 3-bromopropylamine hydrobromide was added and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was extracted with ethyl acetate. The extract was separated and dried and the solvent was distilled off. To a solution of 900 mg of the residue and 0.92 ml (6.59 mmol) of triethylamine in 10 ml of methylene chloride was added 1.25 ml (6.04 mmol) of capryl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with hexane and dried to obtain 1.06 g of the desired compound (60.0%, colorless powder), mp: 41.0-42.0°C.

Anal. for  $C_{18}H_{30}N_2OS$ .

Calcd.: C; 67.04, H; 9.38, N; 8.69

Found: C; 66.82, H; 9.46, N; 8.79

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.88 (3H, t, J=7Hz), 1.26 (12H, m), 1.61 (2H, quint., J=7Hz), 1.85 (2H, quint., J=7Hz), 2.16 (2H, t, J=7Hz), 2.96 (2H, t, J=7Hz), 3.38 (2H, q, J=7Hz), 5.60 (1H, m), 7.23 (1H, dd, J=8, 5Hz), 7.66 (1H, dt, J=8, 2Hz), 8.44 (1H, dd, J=5, 2Hz), 8.58 (1H, d, J=2Hz)

IR (KBr)  $cm^{-1}$ : 3300, 3070, 1640

## Example 3

### Synthesis of 2-[3-(caprylamino)propylthio]pyridine

#### i) Synthesis of 2-(3-aminopropylthio)pyridine dihydrochloride

2-Mercaptopyridine (5.55 g, 50.0 mmol) was dissolved in 1N aqueous solution of sodium hydroxide (150 ml, 150 mmol) and 10.9 g (50.0 mmol) of 3-bromopropylamine hydrobromide was added and the mixture was heated at 60°C for 1 hour. After cooling, the reaction mixture was extracted with ethyl acetate. The extract was separated and dried and the solvent was distilled off. The residue was treated with 10% hydrogen chloride solution in methanol, and the solvent was distilled off. The resulting crystals were washed with acetone, and dried to obtain 10.0 g of the desired compound (82.9%, colorless powder), mp: 167.0-169.0°C.

Anal. for  $C_8H_{14}N_2SCl_2 \cdot 0.2H_2O$ .

Calcd.: C; 39.25, H; 5.93, N; 11.44

Found: C; 39.44, H; 5.78, N; 11.50

#### ii) Synthesis of 2-[3-(caprylamino)propylthio]pyridine

To a solution of 2.41 g (10.0 mmol) of 2-(3-aminopropylthio)pyridine dihydrochloride and 5.02 ml (36.0 mmol) of triethylamine in 100 ml of methylene chloride was added 2.49 ml (12.0 mmol) of capryl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with hexane, and dried to obtain 2.60 g of the desired compound (80.6%, yellow powder).

Anal. for  $C_{18}H_{30}N_2OS$ .

Calcd.: C; 67.04, H; 9.38, N; 8.69

Found: C; 67.04, H; 9.67, N; 8.42

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.87 (3H, t,  $J=7\text{Hz}$ ), 1.26 (12H, m), 1.65 (2H, quint.,  $J=7\text{Hz}$ ), 1.90 (2H, quint.,  $J=7\text{Hz}$ ), 2.21 (2H, t,  $J=7\text{Hz}$ ), 3.25 (2H, t,  $J=7\text{Hz}$ ), 3.38 (2H, q,  $J=7\text{Hz}$ ), 6.50 (1H, m), 7.01 (1H, dd,  $J=8, 5\text{Hz}$ ), 7.21 (1H, d,  $J=8\text{Hz}$ ), 7.50 (1H, td,  $J=8, 2\text{Hz}$ ), 8.41 (1H, dd,  $J=5, 2\text{Hz}$ )  
 IR (Neat)  $\text{cm}^{-1}$ : 3290, 3070, 1640

5

Example 4

## Synthesis of 2-(2-phthalimidoethylthio)pyridine

10 Triethylamine [12.54 ml (90 mmol)] was added to a suspension of 6.67 g (60 mmol) of 2-mercaptopyridine and 15.24 g (60 mmol) of N-(2-bromoethyl)phthalimide in 200 ml of ethanol and stirred at room temperature for 24 hours. The mixture was heated under reflux for 2 hours. The solvent was distilled off, chloroform was added to the residue, and the mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/n-  
 15 hexane=1:2) to obtain 8.00 g of the desired compound (46.9%, colorless crystals).

NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.50 (2H, t,  $J=6\text{Hz}$ ), 3.72 (2H, t,  $J=6\text{Hz}$ ), 6.90 (1H, m), 7.16 (1H, m), 7.43 (1H, m), 7.60-7.93 (4H, m), 8.35 (1H, m)

Example 5

20

## Synthesis of 4-[3-(caprylamino)propylsulfinyl]pyridine

To a solution of 800 mg (2.81 mmol) of 4-[3-(t-butoxycarbonylamino)propylsulfinyl]pyridine in 2 ml of methanol was added 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol) and the mixture was stirred at  
 25 room temperature for 2 hours. The solvent was distilled off. To a solution of 740 mg of the residue and 1.88 ml (13.5 mmol) of triethylamine in 30 ml of chloroform was added 0.70 ml (3.37 mmol) of capryl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain  
 30 780 mg of the desired compound (81.9%, colorless powder), mp: 78.0-79.0°C.

Anal. for  $\text{C}_{18}\text{H}_{30}\text{N}_2\text{O}_2\text{S}$ ,

Calcd.: C; 63.87, H; 8.93, N; 8.27

Found: C; 64.02, H; 9.14, N; 8.21

35 NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t,  $J=7\text{Hz}$ ), 1.26 (12H, m), 1.61 (2H, quint.,  $J=7\text{Hz}$ ), 1.86 (1H, sextet,  $J=7\text{Hz}$ ), 2.06 (1H, sextet,  $J=7\text{Hz}$ ), 2.17 (2H, t,  $J=7\text{Hz}$ ), 2.81 (2H, dt,  $J=14, 7\text{Hz}$ ), 3.01 (1H, dt,  $J=14, 7\text{Hz}$ ), 3.40 (2H, q,  $J=7\text{Hz}$ ), 3.41 (2H, q,  $J=7\text{Hz}$ ), 5.99 (1H, m), 7.53 (2H, dd,  $J=5, 2\text{Hz}$ ), 8.79 (2H, dd,  $J=5, 2\text{Hz}$ )

IR (KBr) $\text{cm}^{-1}$ : 3310, 3060, 1640, 1600

Example 6

40

## Synthesis of 4-[3-(caprylamino)propylsulfonyl]pyridine

To a solution of 800 mg (2.66 mmol) of 4-[3-(t-butoxycarbonylamino)propylsulfonyl]pyridine in 2 ml of methanol was added 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol) and the mixture was stirred at  
 45 room temperature for 2 hours. The solvent was distilled off. To a solution of 670 mg of the residue and 1.92 ml (12.8 mmol) of triethylamine in 30 ml of chloroform was added 0.66 ml (3.19 mmol) of capryl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain  
 50 690 mg of the desired compound (73.2%, colorless powder), mp: 100.0-101.0°C.

Anal. for  $\text{C}_{18}\text{H}_{30}\text{N}_2\text{O}_3\text{S}$ ,

Calcd.: C; 60.98, H; 8.53, N; 7.90

Found: C; 61.08, H; 8.68, N; 7.86

55 NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t,  $J=7\text{Hz}$ ), 1.26 (12H, m), 1.59 (2H, quint.,  $J=7\text{Hz}$ ), 1.99 (2H, quint.,  $J=7\text{Hz}$ ), 2.16 (2H, t,  $J=7\text{Hz}$ ), 3.17 (2H, t,  $J=7\text{Hz}$ ), 3.40 (2H, q,  $J=7\text{Hz}$ ), 5.75 (1H, m), 7.77 (2H, dd,  $J=5, 2\text{Hz}$ ), 8.93 (2H, dd,  $J=5, 2\text{Hz}$ )

IR (KBr) $\text{cm}^{-1}$ : 3330, 1640

Example 7

## Synthesis of 4-[2-(caprylamino)ethylthio]pyridine

5 4-Mercaptopyridine (1.11 g, 10.0 mmol) was dissolved in 1N aqueous solution of sodium hydroxide (40 ml, 40.0 mmol) and 2.46 g (12.0 mmol) of 3-bromopropylamine hydrobromide was added. The mixture was heated with stirring at 60°C for 1 hour. After cooling, the reaction mixture was extracted with ethyl acetate. The extract was washed with 1N aqueous solution of sodium hydroxide and water and dried. The solvent was distilled off to obtain 350 mg of yellow oil. To a solution of the free base thus obtained and 0.38 ml (2.72 mmol) of triethylamine in 30 ml of methylene chloride was added 0.57 ml (2.72 mmol) of capryl chloride under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction solution was washed with 1N aqueous solution of sodium hydroxide and water and dried. The solvent was distilled off. The residue was washed with ether to obtain 360 mg of the desired compound (11.7%, pale yellow powder), mp: 76.0-77.0°C.

Anal. for  $C_{17}H_{28}N_2OS$ ,

15 Calcd.: C; 66.19, H; 9.15, N; 9.08

Found: C; 65.98, H; 9.29, N; 8.70

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.88 (3H, t, J=7Hz), 1.26 (12H, m), 1.62 (2H, quint., J=7Hz), 2.17 (2H, t, J=7Hz), 3.17 (2H, t, J=7Hz), 3.54 (2H, q, J=7Hz), 5.92 (1H, m), 7.21 (2H, dd, J=5, 2Hz), 8.42 (2H, dd, J=5, 2Hz)

20 IR (KBr)  $cm^{-1}$ : 3270, 3090, 1630, 1570

Example 8

## Synthesis of 4-[4-(caprylamino)butylthio]pyridine

25 i) Synthesis of N-(4-hydroxybutyl)caprylamide

To a solution of 2.00 g (22.4 mmol) of 4-amino-1-butanol and 3.75 ml (26.0 mmol) of triethylamine in 50 ml of methylene chloride was added 5.59 ml (26.9 mmol) of capryl chloride and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed successively with 1N aqueous solution of sodium hydroxide, water, 1N hydrochloric acid and water and dried. The solvent was distilled off. The residue was washed with hexane to obtain 4.27 g of the desired compound (78.2%, colorless powder), mp: 76.0-77.0°C.

Anal. for  $C_{14}H_{29}NO_2$ ,

Calcd.: C; 69.09, H; 12.01, N; 5.75

35 Found: C; 69.32, H; 12.31, N; 5.63

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.87 (3H, t, J=6Hz), 1.26 (12H, m), 1.60 (6H, m), 2.16 (2H, t, J=7Hz), 3.29 (2H, q, J=6Hz), 3.68 (2H, t, J=6Hz), 5.74 (1H, m)

IR (KBr)  $cm^{-1}$ : 3380, 3300, 3060, 1640

40 ii) Synthesis of N-(4-methanesulfonyloxybutyl)caprylamide

To a solution of 2.00 g (8.22 mmol) of N-(4-hydroxybutyl)caprylamide and 1.37 ml (9.86 mmol) of triethylamine in 50 ml of methylene chloride was added 0.76 ml (9.86 mmol) of methanesulfonyl chloride under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was washed with hexane to obtain 2.55 g of the desired compound (96.5%, colorless powder), mp: 59.0-60.0°C.

Anal. for  $C_{15}H_{31}NO_4S \cdot 0.7H_2O$ ,

Calcd.: C; 53.93, H; 9.77, N; 4.19

50 Found: C; 53.76, H; 9.64, N; 4.25

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.88 (3H, t, J=6Hz), 1.26 (12H, m), 1.50-1.90 (6H, m), 2.21 (2H, t, J=7Hz), 3.02 (3H, s), 3.31 (2H, q, J=6Hz), 4.26 (2H, t, J=6Hz), 6.00 (1H, m)

IR (KBr)  $cm^{-1}$ : 3310, 2920, 1630

55 iii) Synthesis of 4-[4-(caprylamino)butylthio]pyridine

4-Mercaptopyridine (415 mg, 3.73 mmol) was dissolved in 30 ml of anhydrous methanol, 4.1M sodium methylate solution in methanol (0.91 ml, 3.71 mmol) was added and the mixture was stirred for 30 minutes. N-(4-

Mesyloxybutyl)-caprylamide (1.00 g, 3.11 mmol) was added and the mixture was refluxed for 3 hours. After cooling, the solvent was distilled off and the residue was dissolved in chloroform. The solution was washed with 1N aqueous solution of sodium hydroxide and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with ether and dried to obtain 990 mg of the desired compound (94.6%, colorless powder), mp: 72.0-73.0°C.

Anal. for  $C_{19}H_{32}N_2OS$ .

Calcd.: C; 67.81, H; 9.58, N; 8.32

Found: C; 67.70, H; 9.73, N; 8.26

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.84 (3H, t, J=7Hz), 1.23 (12H, m), 1.40-1.90 (6H, m), 2.12 (2H, t, J=7Hz), 2.97 (2H, t, J=7Hz), 3.27 (2H, q, J=7Hz), 5.48 (1H, m), 7.07 (2H, dd, J=5, 2Hz), 8.35 (2H, dd, J=5, 2Hz)

IR (KBr) $cm^{-1}$ : 3290, 3100, 1630, 1570

#### Example 9

#### 15 Synthesis of 4-[5-(caprylamino)pentylthio]pyridine

##### i) Synthesis of N-(5-hydroxypentyl)caprylamide

To a solution of 2.00 g (19.4 mmol) of 5-amino-1-pentanol and 3.24 ml (23.3 mmol) of triethylamine in 50 ml of methylene chloride was added 4.83 ml (23.3 mmol) of capryl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed successively with 1N aqueous solution of sodium hydroxide, water, 1N hydrochloric acid and water and dried. The solvent was distilled off. The residue was washed with hexane to obtain 4.38 g of the desired compound (87.8%, colorless powder), mp: 62.0-63.0°C.

Anal. for  $C_{15}H_{30}NO_2$ .

Calcd.: C; 69.99, H; 12.14, N; 5.44

Found: C; 70.53, H; 12.36, N; 5.05

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.88 (3H, t, J=6Hz), 1.26 (12H, m), 1.30-1.85 (8H, m), 2.15 (2H, t, J=7Hz), 3.26 (2H, q, J=6Hz), 3.65 (2H, t, J=6Hz), 5.55 (1H, m)

IR (KBr) $cm^{-1}$ : 3400, 3310, 3060, 1630

##### ii) Synthesis of N-(5-methanesulfonyloxypentyl)caprylamide

To a solution of 2.00 g (7.77 mmol) of N-(5-hydroxypentyl)caprylamide and 1.30 ml (9.32 mmol) of triethylamine in 50 ml of methylene chloride was added 0.72 ml (9.32 mmol) of methanesulfonyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was washed with hexane to obtain 1.95 g of the desired compound (74.8%, colorless powder), mp: 67.0-68.0°C.

Anal. for  $C_{16}H_{33}NO_4S$ .

Calcd.: C; 57.28, H; 9.91, N; 4.17

Found: C; 57.13, H; 10.18, N; 4.23

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.88 (3H, t, J=6Hz), 1.26 (12H, m), 1.30-1.90 (8H, m), 2.16 (2H, t, J=7Hz), 3.02 (3H, s), 3.31 (2H, q, J=6Hz), 4.26 (2H, t, J=6Hz), 6.00 (1H, m)

IR (KBr) $cm^{-1}$ : 3330, 3040, 2920, 1640

##### iii) Synthesis of 4-[5-(caprylamino)pentylthio]pyridine

4-Mercaptopyridine (397 mg, 3.58 mmol) was dissolved in 30 ml of anhydrous methanol and 4.1M sodium methylate solution in methanol (0.87 ml, 3.58 mmol) was added. The mixture was stirred for 30 minutes. N-(5-Methanesulfonyloxypentyl)caprylamide (1.00 g, 2.98 mmol) was added and refluxed for 3 hours. After cooling, the solvent was distilled off and the residue was dissolved in chloroform. The solution was washed with 1N aqueous solution of sodium hydroxide and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with ether and dried to obtain 860 mg of the desired compound (82.3%, colorless powder), mp: 60.0-61.0°C.

Anal. for  $C_{20}H_{34}N_2OS$ .

Calcd.: C; 68.52, H; 9.78, N; 7.99

Found: C; 68.49, H; 9.94, N; 7.95

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t,  $J=7\text{Hz}$ ), 1.26 (12H, m), 1.40-1.90 (8H, m), 2.16 (2H, t,  $J=7\text{Hz}$ ), 2.97 (2H, t,  $J=7\text{Hz}$ ), 3.27 (2H, q,  $J=7\text{Hz}$ ), 5.51 (1H, m), 7.10 (2H, dd,  $J=5, 2\text{Hz}$ ), 8.39 (2H, dd,  $J=5, 2\text{Hz}$ )  
 IR (KBr) $\text{cm}^{-1}$ : 3310, 3050, 1630, 1580

## 5 Preparation 10

### Synthesis of 4-[6-(caprylamino)hexylthio]pyridine

#### i) Synthesis of N-(6-hydroxyhexyl)caprylamide

10

To a solution of 2.00 g (17.1 mmol) of 6-amino-1-hexanol and 2.85 ml (20.5 mmol) of triethylamine in 50 ml of methylene chloride was added 4.83 ml (23.3 mmol) of capryl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed successively with 1N aqueous solution of sodium hydroxide, water, 1N hydrochloric acid and water and dried. The solvent was distilled off. The residue was washed with hexane to obtain 4.56 g of the desired compound (98.4%, colorless powder), mp: 77.0-78.0°C.

Anal. for  $\text{C}_{16}\text{H}_{33}\text{NO}_2$ ,

Calcd.: C; 70.80, H; 12.25, N; 5.16

Found: C; 70.94, H; 12.55, N; 5.02

20

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t,  $J=6\text{Hz}$ ), 1.26 (12H, m), 1.20-1.85 (10H, m), 2.15 (2H, t,  $J=7\text{Hz}$ ), 3.25 (2H, q,  $J=6\text{Hz}$ ), 3.64 (2H, t,  $J=6\text{Hz}$ ), 5.49 (1H, m)

IR (KBr) $\text{cm}^{-1}$ : 3390, 3310, 3060, 1640

#### ii) Synthesis of N-(6-mesyloxyhexyl)caprylamide

25

To a solution of 2.00 g (7.37 mmol) of N-(6-hydroxyhexyl)caprylamide and 1.23 ml of triethylamine in 50 ml of methylene chloride was added 0.68 ml (8.84 mmol) of methanesulfonyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was washed with hexane to obtain 2.54 g of the desired compound (98.6%, colorless powder), mp: 62.0-63.0°C.

Anal. for  $\text{C}_{17}\text{H}_{35}\text{NO}_4\text{S}\cdot 0.7\text{H}_2\text{O}$ ,

Calcd.: C; 56.38, H; 10.13, N; 3.87

Found: C; 56.28, H; 10.03, N; 3.94

35

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t,  $J=6\text{Hz}$ ), 1.27 (12H, m), 1.05-1.92 (10H, m), 2.20 (2H, t,  $J=7\text{Hz}$ ), 3.01 (3H, s), 3.26 (2H, q,  $J=6\text{Hz}$ ), 4.23 (2H, t,  $J=6\text{Hz}$ ), 5.72 (1H, m)

IR (KBr) $\text{cm}^{-1}$ : 3320, 3040, 2920, 1630

#### iii) Synthesis of 4-[6-(caprylamino)hexylthio]pyridine

40

4-Mercaptopyridine (381 mg, 3.43 mmol) was dissolved in 30 ml of anhydrous methanol and 4.1M sodium methylate solution in methanol (0.84 ml, 3.43 mmol) was added thereto. The mixture was stirred for 30 minutes. N-(6-methanesulfonyloxyhexyl)caprylamide (1.00 g, 2.86 mmol) was added and refluxed for 3 hours. After cooling, the solvent was distilled off, the residue was dissolved in chloroform. The solution was washed with 1N aqueous solution of sodium hydroxide and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with ether, and dried to obtain 870 mg of the desired compound (87.4%, colorless powder), mp: 72.0-73.0°C.

Anal. for  $\text{C}_{21}\text{H}_{36}\text{N}_2\text{OS}$ ,

Calcd.: C; 69.18, H; 9.95, N; 7.68

50

Found: C; 69.14, H; 10.13, N; 7.61

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t,  $J=7\text{Hz}$ ), 1.26 (12H, m), 1.00-2.00 (10H, m), 2.15 (2H, t,  $J=7\text{Hz}$ ), 2.97 (2H, t,  $J=7\text{Hz}$ ), 3.25 (2H, q,  $J=7\text{Hz}$ ), 5.48 (1H, m), 7.10 (2H, dd,  $J=5, 2\text{Hz}$ ), 8.38 (2H, dd,  $J=5, 2\text{Hz}$ )

IR (KBr) $\text{cm}^{-1}$ : 3290, 3100, 2920, 2850, 1630, 1570

55

Example 11

## Synthesis of 4-[4 (caprylpiperidyl)thio]pyridine

## 5 i) Synthesis of N-t-butoxycarbonyl-4 methanesulfonyloxypiperidine

To a solution of 1.00 g (4.97mmol) of N-t-butoxycarbonyl-4-hydroxypiperidine and 0.83 ml (5.96 mmol) of triethylamine in 50 ml of methylene chloride was added 0.46 ml (5.96 mmol) of methanesulfonyl chloride under ice-cooling and stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture  
 10 was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was washed with hexane to obtain 1.37 g of the desired compound (98.6%, colorless powder), mp: 87.0-88.0°C.

Anal. for  $C_{11}H_{21}NO_5S$ .

Calcd.: C; 47.29, H; 7.58, N; 5.01

15 Found: C; 47.04, H; 7.76, N; 5.06

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.46 (9H, s), 1.70-2.08 (4H, m), 3.04 (3H, s), 3.30 (2H, ddd, J=14, 8, 4Hz), 3.71 (2H, ddd, J=14, 7, 4Hz), 4.88 (1H, septet, J=4Hz)

IR (KBr) $cm^{-1}$ : 2960, 2850, 1690, 1680

## 20 ii) Synthesis of 4-[4-(t-butoxycarbonyl)piperidylthio]pyridine

4-Mercaptopyridine (362 mg, 3.26 mmol) was dissolved in 30 ml of anhydrous methanol and 4.1M sodium methylate solution in methanol (0.80 ml, 3.26 mmol) was added. The mixture was stirred for 30 minutes. N-t-Butoxycarbonyl-4-methanesulfonyloxypiperidine (760 mg, 2.72 mmol) was added and the mixture was refluxed  
 25 for 18 hours. After cooling, the solvent was distilled off. The residue was dissolved in ethyl acetate and was washed with 1N aqueous solution of sodium hydroxide and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: hexane/ethyl acetate=1:1) to obtain 660 mg of the desired compound (82.4%, colorless powder), mp: 71.0-72.0°C.

Anal. for  $C_{15}H_{22}N_2O_2S$ .

30 Calcd.: C; 61.19, H; 7.53, N; 9.51

Found: C; 61.28, H; 7.64, N; 9.39

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.46 (9H, s), 1.50-1.80 (2H, m), 2.03 (2H, ddd, J=14, 9, 4Hz), 3.61 (2H, ddd, J=14, 10, 4Hz), 3.56 (1H, tt, J=10, 4Hz), 3.96 (2H, dt, J=14, 4Hz), 7.14 (2H, dd, J=5, 2Hz), 8.42 (2H, dd, J=5, 2Hz)

35 IR (KBr) $cm^{-1}$ : 2960, 2930, 2850, 1690, 1580

## iii) Synthesis of 4-[4-(caprylpiperidyl)thio]pyridine

To a solution of 250 mg (0.85 mmol) of 4-[4-(N-t-butoxycarbonyl)piperidylthio]pyridine in 5 ml of methanol  
 40 was added of 2N hydrogen chloride solution in methanol (5 ml, 10 mmol) and the mixture was stirred at room temperature for 1 hour. The solvent was distilled off. To a solution of 225 mg of the residue and 0.42 ml (3.03 mmol) of triethylamine in 5 ml of methylene chloride was added 0.21 ml (1.01 mmol) of capryl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture  
 45 was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 210 mg of the desired compound (71.7%, colorless oil).

Anal. for  $C_{20}H_{32}N_2OS \cdot 0.5H_2O$ .

Calcd.: C; 67.18, H; 9.30, N; 7.83

Found: C; 67.33, H; 9.19, N; 7.71

50 NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.88 (3H, t, J=7Hz), 1.27 (12H, m), 1.50-1.90 (4H, m), 2.00-2.20 (2H, m), 2.33 (2H, t, J=7Hz), 3.10 (1H, td, J=12, 3Hz), 3.27 (1H, td, J=12, 3Hz), 3.59 (1H, m), 3.83 (1H, dt, J=14, 3Hz), 4.32 (1H, dt, J=14, 3Hz), 7.16 (2H, dd, J=5, 2Hz), 8.44 (2H, brd, J=5Hz)

IR (Neat)  $cm^{-1}$ : 3270, 3100, 1630, 1570

Example 12

## Synthesis of 3-(4-phthalimidobutylthio)pyridine

5 To a solution of 3.64 g (20 mmol) of 3-dimethylaminocarbonylthiopyridine in 100 ml of methanol was added 1.6 g (40 mmol) of sodium hydroxide. The mixture was heated and refluxed for 3 hours under nitrogen atmosphere. After cooling, 5.64 g (20 mmol) of N-(4-bromobutyl)phthalimide was added. The mixture was heated and refluxed for 2.5 hours. The solvent was distilled off and chloroform was added to the residue. The mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/n-hexane=1:1) to obtain 280 mg of the desired compound (4.5%, colorless oil).

10 NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.47-2.05 (4H, m), 2.95 (2H, t, J=7Hz), 3.68 (2H, t, J=7Hz), 7.16 (1H, dd, J=7, 4Hz), 7.54-7.95 (5H, m), 8.38 (1H, dd, J=5, 2Hz); 8.54 (1H, d)

Example 13

## Synthesis of 4-[3-(propionylamino)propylthio]pyridine

20 To a solution of 700 mg (2.90 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 1.62 ml (11.6 mmol) of triethylamine in 30 ml of methylene chloride was added 0.30 ml (3.48 mmol) of propionyl chloride and the mixture was stirred at room temperature for 30 minutes. The reaction solution was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain the powder which was washed with ether and dried to obtain 483 mg of the desired compound (74.2%, yellow prisms), mp: 50.0-51.0°C.

25 Anal. for  $\text{C}_{11}\text{H}_{16}\text{N}_2\text{OS}$ .

Calcd.: C; 58.90, H; 7.19, N; 12.49

Found: C; 58.59, H; 7.25, N; 12.33

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.16 (3H, t, J=7Hz), 1.94 (2H, quint., J=7Hz), 2.22 (2H, q, J=7Hz), 3.01 (2H, t, J=7Hz), 3.42 (2H, q, J=7Hz), 5.80 (1H, m), 7.11 (2H, dd, J=5, 2Hz), 8.39 (2H, dd, J=5, 2Hz).

30 IR (KBr) $\text{cm}^{-1}$ : 3310, 3080, 1640, 1580

Example 14

## Synthesis of 4-[3-(butyrylamino)propylthio]pyridine

35 To a solution of 700 mg (2.90 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 1.62 ml (11.6 mmol) of triethylamine in 30 ml of methylene chloride was added 0.36 ml (3.48 mmol) of butyryl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:1) to obtain 630 mg of the desired compound (91.1%, pale yellow oil).

Anal. for  $\text{C}_{12}\text{H}_{18}\text{N}_2\text{OS} \cdot 0.1\text{H}_2\text{O}$ .

Calcd.: C; 60.02, H; 7.64, N; 11.66

Found: C; 60.01, H; 7.86, N; 11.39

45 NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.95 (3H, t, J=7Hz), 1.67 (2H, sextet., J=7Hz), 1.93 (2H, quint., J=7Hz), 2.16 (2H, t, J=7Hz), 3.01 (2H, t, J=7Hz), 3.42 (2H, q, J=7Hz), 5.70 (1H, m), 7.11 (2H, dd, J=5, 2Hz), 8.40 (2H, dd, J=5, 2Hz)

IR (KBr) $\text{cm}^{-1}$ : 3310, 3080, 1640, 1570

Example 15

## Synthesis of 4-[3-(hexanoylamino)propylthio]pyridine

55 To a solution of 600 mg (2.49 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 1.39 ml (9.96 mmol) of triethylamine in 25 ml of methylene chloride was added 0.42 ml (2.99 mmol) of hexanoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain

542 mg of the desired compound (81.7%, pale yellow oil).

Anal. for  $C_{14}H_{22}N_2OS \cdot 0.7H_2O$ .

Calcd.: C; 60.27, H; 8.45, N; 10.04

Found: C; 60.45, H; 8.19, N; 9.95

5 NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.89 (3H, t, J=7Hz), 1.10-1.50 (4H, m), 1.63 (2H, quint., J=7Hz), 1.93 (2H, quint., J=7Hz), 2.18 (2H, t, J=7Hz), 3.01 (2H, t, J=7Hz), 3.41 (2H, q, J=7Hz), 5.78 (1H, m), 7.10 (2H, dd, J=5, 2Hz), 8.39 (2H, dd, J=5, 2Hz)

IR (Neat)  $cm^{-1}$ : 3280, 3070, 1650, 1570

#### 10 Example 16

##### Synthesis of 4-[3-(caproylamino)propylthio]pyridine

To a solution of 1.21 g (5.00 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.79 ml (20.0 mmol) of triethylamine in 50 ml of methylene chloride was added 1.02 ml (6.00 mmol) of caproyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with hexane and dried to obtain 1.24 g of the desired compound (84.2%, colorless powder), mp: 48.0-49.0°C.

Anal. for  $C_{16}H_{26}N_2OS$ .

Calcd.: C; 65.26, H; 8.90, N; 9.51

Found: C; 65.35, H; 9.07, N; 9.42

25 NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.87 (3H, t, J=7Hz), 1.27 (8H, m), 1.62 (2H, quint., J=7Hz), 1.93 (2H, quint., J=7Hz), 2.18 (2H, t, J=7Hz), 3.01 (2H, t, J=7Hz), 3.41 (2H, q, J=7Hz), 5.70 (1H, m), 7.10 (2H, dd, J=5, 2Hz), 8.40 (2H, dd, J=5, 2Hz)

IR (KBr)  $cm^{-1}$ : 3300, 3070, 1640, 1580

#### 30 Example 17

##### Synthesis of 4-[3-(lauroylamino)propylthio]pyridine

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.77 ml (19.8 mmol) of triethylamine in 40 ml of methylene chloride was added 1.15 ml (4.96 mmol) of lauroyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with hexane and dried to obtain 1.05 g of the desired compound (72.2%, colorless powder), mp: 71.0-72.0°C.

Anal. for  $C_{20}H_{34}N_2OS$ .

Calcd.: C; 68.52, H; 9.78, N; 7.99

Found: C; 68.62, H; 10.00, N; 7.91

45 NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.88 (3H, t, J=7Hz), 1.25 (16H, m), 1.62 (2H, quint., J=7Hz), 1.93 (2H, quint., J=7Hz), 2.17 (2H, t, J=7Hz), 3.01 (2H, t, J=7Hz), 3.41 (2H, q, J=7Hz), 5.71 (1H, m), 7.10 (2H, dd, J=5, 2Hz), 8.39 (2H, dd, J=5, 2Hz)

IR (KBr)  $cm^{-1}$ : 3290, 3070, 1640, 1580

#### Example 18

##### 50 Synthesis of 4-[3-(myristoylamino)propylthio]pyridine

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.77 ml (19.8 mmol) of triethylamine in 40 ml of methylene chloride was added 1.22 ml (4.96 mmol) of myristoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with hexane and dried to obtain 1.17 g of the desired compound (74.5%, colorless powder), mp: 80.0-81.0°C.



Anal. for  $C_{22}H_{38}N_2OS$ ,

Calcd.: C; 69.79, H; 10.12, N; 7.40

Found: C; 69.79, H; 10.32, N; 7.32

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.88 (3H, t, J=7Hz), 1.25 (20H, m), 1.62 (2H, quint., J=7Hz), 1.93 (2H, quint., J=7Hz), 2.17 (2H, t, J=7Hz), 3.01 (2H, t, J=7Hz), 3.41 (2H, q, J=7Hz), 5.67 (1H, m), 7.10 (2H, dd, J=5, 2Hz), 8.39 (2H, dd, J=5, 2Hz)

IR (KBr) $cm^{-1}$ : 3300, 3080, 1640, 1570

#### Example 19

##### Synthesis of 4-[3-(palmitoylamino)propylthio]pyridine

To a solution of 1.21 g (5.00 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.79 ml (20.0 mmol) of triethylamine in 50 ml of methylene chloride was added 1.65 ml (6.00 mmol) of palmitoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with hexane and dried to obtain 1.50 g of the desired compound (73.8%, colorless powder), mp: 84.0-85.0°C.

Anal. for  $C_{24}H_{42}N_2OS$ ,

Calcd.: C; 70.88, H; 10.41, N; 6.89

Found: C; 70.89, H; 10.64, N; 6.81

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.88 (3H, t, J=7Hz), 1.25 (20H, m), 1.62 (2H, quint., J=7Hz), 1.93 (2H, quint., J=7Hz), 2.17 (2H, t, J=7Hz), 3.00 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz), 5.69 (1H, m), 7.09 (2H, dd, J=5, 2Hz), 8.40 (2H, dd, J=5, 2Hz)

IR (KBr) $cm^{-1}$ : 3300, 3070, 1640, 1570

#### Example 20

##### Synthesis of 4-[3-(stearoylamino)propylthio]pyridine

To a solution of 700 mg (2.90 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 1.62 ml (11.6 mmol) of triethylamine in 30 ml of methylene chloride was added 1.18 ml (3.48 mmol) of stearoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with hexane and dried to obtain 1.20 g of the desired compound (95.2%, colorless powder), mp: 88.0-89.0°C.

Anal. for  $C_{26}H_{46}N_2OS$ ,

Calcd.: C; 70.88, H; 10.41, N; 6.89

Found: C; 70.89, H; 10.64, N; 6.81

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.88 (3H, t, J=7Hz), 1.25 (20H, m), 1.62 (2H, quint., J=7Hz), 1.93 (2H, quint., J=7Hz), 2.17 (2H, t, J=7Hz), 3.03 (2H, t, J=7Hz), 3.41 (2H, q, J=7Hz), 5.63 (1H, m), 7.10 (2H, dd, J=5, 2Hz), 8.40 (2H, dd, J=5, 2Hz)

IR (KBr) $cm^{-1}$ : 3290, 3070, 1640, 1570

#### Example 21

##### Synthesis of 4-[3-(oleoylamino)propylthio]pyridine

To a solution of 700 mg (2.90 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 1.62 ml (11.6 mmol) of triethylamine in 30 ml of methylene chloride was added 1.55 ml (3.48 mmol) of oleoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with hexane and dried to obtain 1.05 g of the desired compound (83.7%, colorless powder), mp: 50.0-50.5°C.

Anal. for  $C_{26}H_{44}N_2OS$ ,

Calcd.: C: 70.70, H: 10.27, N: 6.38

Found: C: 70.83, H: 10.35, N: 6.42

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, t, J=7Hz), 1.26 (20H, m), 1.66 (2H, quint., J=7Hz), 1.70-2.10 (6H, m), 2.17 (2H, t, J=7Hz), 3.00 (2H, t, J=7Hz), 3.41 (2H, q, J=7Hz), 5.34 (2H, t, J=6Hz), 5.63 (1H, m), 7.10 (2H, dd, J=5, 2Hz), 8.39 (2H, dd, J=5, 2Hz)

IR (KBr) $\text{cm}^{-1}$ : 3300, 3070, 1640, 1570

#### Example 22

##### 10 Synthesis of 4-[3-(2-ethylhexanoylamino)propylthio]pyridine hydrochloride

To a solution of 800 mg (3.32 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.22 ml (15.9 mmol) of triethylamine in 30 ml of methylene chloride was added 0.69 ml (3.98 mmol) of 2-ethylhexanoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 1.02 g of the desired compound (free base) (quant., pale yellow oil).

Anal. for  $\text{C}_{16}\text{H}_{26}\text{N}_2\text{OS} \cdot 0.4\text{H}_2\text{O}$ ,

Calcd.: C: 63.71, H: 8.96, N: 9.29

20 Found: C: 64.06, H: 9.16, N: 8.74

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.87 (3H, t, J=7Hz), 0.88 (3H, t, J=7Hz), 1.00-1.75 (8H, m), 1.91 (1H, quint., J=7Hz), 1.94 (2H, quint., J=7Hz), 3.02 (2H, t, J=7Hz), 3.43 (2H, q, J=7Hz), 5.70 (1H, m), 7.11 (2H, dd, J=5, 2Hz), 8.39 (2H, dd, J=5, 2Hz)

IR (neat)  $\text{cm}^{-1}$ : 3290, 3050, 2960, 1640

25 The above free base (250 mg, 0.81 mmol) was treated with 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol). The solvent was distilled off. The powder was washed with acetone and dried to obtain 280 mg of the desired compound (quant., colorless powder), mp: 163.0-165.0°C

Anal. for  $\text{C}_{16}\text{H}_{27}\text{N}_2\text{OSCl} \cdot 0.2\text{H}_2\text{O}$ ,

Calcd.: C: 57.45, H: 8.26, N: 8.37

30 Found: C: 57.78, H: 8.32, N: 8.31

#### Example 23

##### 35 Synthesis of 4-[3-(cyclohexanoylamino)propylthio] pyridine hydrochloride

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.77 ml (19.8 mmol) of triethylamine in 40 ml of methylene chloride was added 0.66 ml (4.96 mmol) of cyclohexanoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 890 mg of the desired compound (free base) (77.0%, colorless prisms), mp: 93.0-94.0°C.

Anal. for  $\text{C}_{15}\text{H}_{22}\text{N}_2\text{OS}$ ,

Calcd.: C: 64.71, H: 7.96, N: 10.06

45 Found: C: 64.88, H: 8.02, N: 10.07

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.10-2.15 (13H, m), 3.00 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz), 5.68 (1H, m), 7.10 (2H, dd, J=5, 2Hz), 8.40 (2H, d, J=5Hz)

IR (KBr) $\text{cm}^{-1}$ : 3290, 3050, 2930, 1630

The above free base (650 mg, 2.33 mmol) was treated with 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol). The solvent was distilled off. The powder was washed with acetone and dried to obtain 670 mg of the desired compound (91.1%, colorless powder).

Anal. for  $\text{C}_{15}\text{H}_{23}\text{N}_2\text{OSCl} \cdot 1.5\text{H}_2\text{O}$ ,

Calcd.: C: 52.69, H: 7.66, N: 8.19

55 Found: C: 52.58, H: 6.95, N: 8.14

Example 24

## Synthesis of 4-[3-(pivaloylamino)propylthio]pyridine hydrochloride

5 To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.77 ml (19.8 mmol) of triethylamine in 40 ml of methylene chloride was added 0.61 ml (4.96 mmol) of pivaloyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 1.01 g of the  
10 desired compound (free base) (96.4%, yellow oil).

Anal. for  $C_{13}H_{20}N_2OS$ .

Calcd.: C; 60.15, H; 8.08, N; 10.79

Found: C; 60.44, H; 7.93, N; 10.66

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.20 (9H, s), 1.94 (2H, quint., J=7Hz), 3.00 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz),  
15 5.85 (1H, m), 7.11 (2H, dd, J=5, 2Hz), 8.40 (2H, dd, J=5, 2Hz)

IR (KBr) $cm^{-1}$ : 3270, 3030, 2980, 1650

The above free base (1.01 g, 4.00 mmol) was treated with 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol). The solvent was distilled off. The powder was washed with acetone and dried to obtain 1.16 g of the desired compound (quant., colorless powder), mp: 87.0-90.0°C.

20 Anal. for  $C_{13}H_{21}N_2OSCl \cdot 2.0H_2O$ .

Calcd.: C; 48.06, H; 7.76, N; 8.62

Found: C; 47.93, H; 7.57, N; 8.53

Example 25

## Synthesis of 4-[3-(trifluoroacetyl amino)propylthio]pyridine hydrochloride

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.77 ml (19.8 mmol) of triethylamine in 40 ml of methylene chloride was added 0.70 ml (4.96 mmol) of anhydrous trifluoroacetic acid under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes.  
30 The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with hexane and dried to obtain 750 mg of the desired compound (free base) (68.4%, pale yellow prisms).

35 Anal. for  $C_{10}H_{11}N_2OSF_3$ .

Calcd.: C; 45.45, H; 4.20, N; 10.60

Found: C; 45.26, H; 4.17, N; 10.52

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.02 (2H, quint., J=7Hz), 3.03 (2H, t, J=7Hz), 3.55 (2H, q, J=7Hz), 7.08 (2H, dd, J=5, 2Hz), 7.34 (1H, m), 8.37 (2H, dd, J=5, 2Hz)

40 IR (KBr) $cm^{-1}$ : 3160, 3030, 2850, 1720, 1590

The above free base (340 mg, 1.29 mmol) was treated with 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol). The solvent was distilled off. The powder was washed with acetone and dried to obtain 367 mg of the desired compound (94.9%, colorless powder), mp: 184.0-186.0°C

Anal. for  $C_{10}H_{12}N_2OSClF_3 \cdot 0.3H_2O$ .

45 Calcd.: C; 39.23, H; 4.15, N; 9.15

Found: C; 39.45, H; 3.99, N; 9.14

Example 26

## Synthesis of 4-[3-(4-phenylbenzoylamino)propylthio]pyridine hydrochloride

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.89 ml (19.9 mmol) of triethylamine in 40 ml of methylene chloride was added 1.08 ml (4.98 mmol) of 4-phenylbenzoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction  
55 solution was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain the powder which was washed with ether and dried to obtain 980 mg of the desired compound (free base) (67.8%, pale yellow powder), mp: 169.0-170.0°C.

Anal. for  $C_{21}H_{20}N_2OS$ ,

Calcd.: C; 72.38, H; 5.78, N; 8.04

Found: C; 72.15, H; 5.84, N; 7.95

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.07 (2H, quint.,  $J=7$ Hz), 3.09 (2H, t,  $J=7$ Hz), 3.65 (2H, q,  $J=7$ Hz), 6.50 (1H, m), 7.12 (2H, dd,  $J=5$ , 2Hz), 7.30-7.90 (9H, m), 8.39 (2H, dd,  $J=5$ , 2Hz)

IR (KBr) $cm^{-1}$ : 3340, 3030, 2930, 1640, 1600

The above free base (500 mg, 1.43 mmol) was treated with 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol). The solvent was distilled off. The powder was washed with acetone and dried to obtain 545 mg of the desired compound (98.7 %, colorless powder), mp: 198.0-200.0°C.

Anal. for  $C_{21}H_{21}N_2OSCl$ ,

Calcd.: C; 65.53, H; 5.50, N; 7.28

Found: C; 65.36, H; 5.52, N; 7.20

#### Example 27

##### Synthesis of 4-[3-(1-naphthoylamino)propylthio]pyridine hydrochloride

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio) pyridine dihydrochloride and 2.78 ml (19.9 mmol) of triethylamine in 40 ml of methylene chloride was added 0.75 ml (4.98 mmol) of 1-naphthoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ ethyl acetate=1:10) to obtain the powder which was washed with ether and dried to obtain 1.00 g of the desired compound (free base) (74.8%, yellow powder), mp: 113.0-114.0°C.

Anal. for  $C_{19}H_{18}N_2OS$ ,

Calcd.: C; 70.78, H; 5.63, N; 8.69

Found: C; 70.55, H; 5.70, N; 8.46

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.09 (2H, quint.,  $J=7$ Hz), 3.11 (2H, t,  $J=7$ Hz), 3.68 (2H, q,  $J=7$ Hz), 6.31 (1H, m), 7.11 (2H, dd,  $J=5$ , 2Hz), 7.35-7.70 (4H, m), 7.80-8.00 (2H, m), 8.20-8.35 (1H, m), 8.39 (2H, dd,  $J=5$ , 2Hz)

IR (KBr) $cm^{-1}$ : 3280, 3050, 2960, 1640, 1610

The above free base (850 mg, 2.64 mmol) was treated with 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol). The solvent was distilled off. The powder was washed with acetone and dried to obtain 930 mg of the desired compound (98.3%, pale yellow powder), mp: 190.0-192.0°C

Anal. for  $C_{19}H_{19}N_2OSCl$ ,

Calcd.: C; 63.59, H; 5.34, N; 7.81

Found: C; 63.45, H; 5.32, N; 7.74

#### Example 28

##### Synthesis of 4-[3-(cinnamoylamino)propylthio]pyridine hydrochloride

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.78 ml (19.9 mmol) of triethylamine in 40 ml of methylene chloride was added 830 mg (4.98 mmol) of cinnamoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain the powder which was washed with ether and dried to obtain 1.10 g of the desired compound (free base) (88.8%, colorless powder), mp: 116.0-117.0°C.

Anal. for  $C_{17}H_{18}N_2OS$ ,

Calcd.: C; 68.43, H; 6.08, N; 9.39

Found: C; 68.26, H; 6.18, N; 9.19

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.01 (2H, quint.,  $J=7$ Hz), 3.05 (2H, t,  $J=7$ Hz), 3.56 (2H, q,  $J=7$ Hz), 6.05 (1H, m), 6.41 (1H, d,  $J=16$ Hz), 7.10 (2H, dd,  $J=5$ , 2Hz), 7.30-7.55 (5H, m), 7.65 (1H, d,  $J=16$ Hz), 8.39 (2H, dd,  $J=5$ , 2Hz)

IR (KBr) $cm^{-1}$ : 3350, 3300, 3030, 1650, 1620, 1570

The above free base (830 mg, 2.78 mmol) was treated with 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol). The solvent was distilled off. The powder was washed with acetone and dried to obtain 950 mg of the desired compound (quant., colorless powder), mp: 105.0-108.0°C.

Anal. for  $C_{17}H_{19}N_2OSCl \cdot 2.0H_2O$ .  
 Calcd.: C: 55.05, H: 6.25, N: 7.55  
 Found: C: 54.95, H: 5.83, N: 7.74

### 5 Example 29

#### Synthesis of 4-[3-(4-chlorobenzoylamino)propylthio]pyridine hydrochloride

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.77 ml (19.8 mmol) of triethylamine in 40 ml of methylene chloride was added 0.63 ml (4.96 mmol) of 4-chlorobenzoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with ether and dried to obtain 1.01 g of the desired compound (free base) (79.3%, pale yellow powder), mp: 95.0-96.0°C.

Anal. for  $C_{15}H_{15}N_2OSCl$ .  
 Calcd.: C: 58.72, H: 4.93, N: 9.13  
 Found: C: 58.64, H: 4.95, N: 9.00

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.05 (2H, quint., J=7Hz), 3.07 (2H, t, J=7Hz), 3.61 (2H, q, J=7Hz), 6.50 (1H, m), 7.10 (2H, dd, J=5, 2Hz), 7.41 (2H, d, J=9Hz), 7.71 (2H, d, J=9Hz), 8.38 (2H, dd, J=5, 2Hz)

IR (KBr)  $cm^{-1}$ : 3280, 3030, 2930, 1630, 1600

The above free base (700 mg, 2.28 mmol) was treated with 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol). The solvent was distilled off. The powder was washed with acetone and dried to obtain 750 mg of the desired compound (95.8%, pale yellow powder), mp: 195.0-197.0°C.

Anal. for  $C_{15}H_{16}OSCl_2 \cdot 0.3H_2O$ .  
 Calcd.: C: 51.67, H: 4.80, N: 8.03  
 Found: C: 51.73, H: 4.80, N: 7.88

### Example 30

#### Synthesis of 4-[3-(4-methoxybenzoylamino)propylthio]pyridine

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.77 ml (19.8 mmol) of triethylamine in 40 ml of methylene chloride was added 846 mg (4.96 mmol) of 4-anisoyl chloride under ice-cooling with stirring and the mixture was stirred for at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with ether and dried to obtain 990 mg of the desired compound (78.9%, colorless powder), mp: 121.0-122.0°C.

Anal. for  $C_{16}H_{18}O_2S$ .  
 Calcd.: C: 63.55, H: 6.00, N: 9.26  
 Found: C: 63.50, H: 6.10, N: 9.14

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.04 (2H, quint., J=7Hz), 3.07 (2H, t, J=7Hz), 3.60 (2H, q, J=7Hz), 3.85 (3H, s), 6.38 (1H, m), 6.92 (2H, dd, J=7, 2Hz), 7.11 (2H, dd, J=5, 2Hz), 7.74 (2H, dd, J=7, 2Hz), 8.38 (2H, dd, J=5, 2Hz)

IR (KBr)  $cm^{-1}$ : 3340, 3030, 2930, 1640, 1600

### Example 31

#### Synthesis of 4-[3-(4-methylbenzoylamino)propylthio]pyridine

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.77 ml (19.8 mmol) of triethylamine in 40 ml of methylene chloride was added 0.65 ml (4.96 mmol) of 4-toluoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain the powder which was washed with ether and dried to obtain 910 mg of the desired compound (76.6%, colorless powder), mp: 110.0-111.0°C.

Anal. for  $C_{16}H_{18}N_2OS$ .

Calcd.: C; 67.10, H; 6.33, N; 9.78

Found: C; 67.25, H; 6.41, N; 9.67

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.04 (2H, quint.,  $J=7$ Hz), 2.39 (3H, s), 3.06 (2H, t,  $J=7$ Hz), 3.61 (2H, q,  $J=7$ Hz),  
 5 6.47 (1H, m), 7.11 (2H, dd,  $J=5, 2$ Hz), 7.23 (2H, d,  $J=8$ Hz), 7.67 (2H, d,  $J=8$ Hz), 8.39 (2H, d,  $J=5, 2$ Hz).  
 IR (KBr)  $cm^{-1}$ : 3330, 3040, 2930, 1630

#### Example 32

##### 10 Synthesis of 4-[3-(4-t-butylbenzoylamino)propylthio]pyridine hydrochloride

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.77 ml (19.8 mmol) of triethylamine in 40 ml of methylene chloride was added 0.48 ml (4.96 mmol) of 4-t-butylbenzoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction  
 15 mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 1.20 g of the desired compound (free base) (88.0%, yellow powder).

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.33 (9H, s), 2.05 (2H, quint.,  $J=7$ Hz), 3.07 (2H, t,  $J=7$ Hz), 3.62 (2H, q,  $J=7$ Hz),  
 20 6.38 (1H, m), 7.11 (2H, dd,  $J=5, 2$ Hz), 7.45 (2H, dd,  $J=7, 2$ Hz), 7.71 (2H, dd,  $J=7, 2$ Hz), 8.39 (2H, dd,  $J=5, 2$ Hz)  
 IR (Neat)  $cm^{-1}$ : 3390, 3270, 2960, 1650, 1600

The above free base (1.20 g, 3.65 mmol) was treated with 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol). The solvent was distilled off. The powder was washed with acetone and dried to obtain 1.33 g of the desired compound (quant., yellow powder)

Anal. for  $C_{19}H_{25}N_2OSCl \cdot 3.5H_2O$ .

25 Calcd.: C; 53.32, H; 7.54, N; 6.55

Found: C; 53.45, H; 7.24, N; 6.57

#### Example 33

##### 30 Synthesis of 4-[3-(3,5-dimethoxybenzoylamino)propylthio]pyridine

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.77 ml (19.8 mmol) of triethylamine in 40 ml of methylene chloride was added 995 mg (4.96 mmol) of 3,5-dimethoxybenzoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The  
 35 reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 1.21 g of the desired compound (87.7%, pale yellow powder), mp: 110.0-111.0°C.

Anal. for  $C_{17}H_{20}N_2O_3S$ ;

Calcd.: C; 61.42, H; 6.06, N; 8.43

40 Found: C; 61.32, H; 6.11, N; 8.24

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.04 (2H, quint.,  $J=7$ Hz), 3.06 (2H, t,  $J=7$ Hz), 3.60 (2H, q,  $J=7$ Hz), 3.82 (6H, s), 6.47 (1H, m), 6.58 (1H, t,  $J=2$ Hz), 6.89 (2H, d,  $J=2$ Hz), 7.11 (2H, dd,  $J=5, 2$ Hz), 8.38 (2H, dd,  $J=5, 2$ Hz)

IR (Neat)  $cm^{-1}$ : 3250, 3060, 2930, 1650, 1590

#### 45 Example 34

##### Synthesis of 4-[3-(4-n-butylbenzoylamino)propylthio]pyridine hydrochloride

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.78 ml (19.9 mmol) of triethylamine in 40 ml of methylene chloride was added 0.93 ml (4.96 mmol) of 4-n-butylbenzoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minute. The reaction  
 50 mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 1.10 g of the desired compound (free base) (80.7%, colorless wax), mp: 46.0-47.0°C.

55 Anal. for  $C_{19}H_{24}N_2OS \cdot 0.3H_2O$ ,

Calcd.: C; 68.35, H; 7.43, N; 8.39

Found: C; 68.36, H; 7.26, N; 8.49

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 0.92 (3H, t,  $J=7$ Hz), 1.35 (2H, sextet,  $J=7$ Hz), 1.60 (2H, quint.,  $J=7$ Hz), 2.05

(4H, quint., J=7Hz), 2.65 (2H, t, J=7Hz), 3.07 (2H, t, J=7Hz), 3.61 (2H, q, J=7Hz), 6.43 (1H, m), 7.12 (2H, dd, J=5, 2Hz), 7.24 (2H, d, J=8Hz), 7.68 (2H, dd, J=5, 2Hz), 8.38 (2H, d, J=8Hz)

IR (KBr)cm<sup>-1</sup>: 3360, 3030, 2920, 1630

The above free base (1.10 g, 3.35 mmol) was treated with 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol). The solvent was distilled off. The powder was washed with acetone and dried to obtain 1.33 g of the desired compound (quant., colorless powder), mp: 77.0-80.0°C

Anal. for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>OSCl·1.0H<sub>2</sub>O,

Calcd.: C; 57.20, H; 6.82, N; 7.02

Found: C; 57.16, H; 6.87, N; 6.91

### Example 35

#### Synthesis of 4-[3-(4-n-butoxybenzoylamino)propylthio]pyridine hydrochloride

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.78 ml (19.9 mmol) of triethylamine in 40 ml of methylene chloride was added 0.94 ml (4.96 mmol) of 4-n-butoxybenzoyl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 1.10 g of the desired compound (free base) (76.9%, colorless powder), mp: 98.0-99.0°C.

Anal. for C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>OS,

Calcd.: C; 66.25, H; 7.02, N; 8.13

Found: C; 66.52, H; 6.99, N; 8.11

NMR (200 MHz, CDCl<sub>3</sub>) δ: 0.98 (3H, t, J=7Hz), 1.49 (2H, sextet., J=7Hz), 1.79 (2H, quint., J=7Hz), 2.04 (2H, quint., J=7Hz), 3.06 (2H, t, J=7Hz), 3.60 (2H, q, J=7Hz), 4.00 (2H, t, J=7Hz), 6.36 (1H, m), 6.91 (2H, dd, J=9, 2Hz), 7.11 (2H, dd, J=5, 2Hz), 7.72 (2H, dd, J=9, 2Hz), 8.38 (2H, dd, J=5, 2Hz)

IR (KBr)cm<sup>-1</sup>: 3360, 3030, 2920, 1630

The above free base (800 mg, 2.32 mmol) was treated with 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol). The solvent was distilled off. The powder was washed with acetone and dried to obtain 880 mg of the desired compound (99.5%, colorless powder), mp: 140.0-142.0°C.

Anal. for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>OSCl·1.0H<sub>2</sub>O,

Calcd.: C; 52.55, H; 5.59, N; 8.17

Found: C; 52.45, H; 5.57, N; 8.02

### Example 36

#### Synthesis of 4-[3-(salicyloylamino)propylthio]pyridine hydrochloride

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.77 ml (19.8 mmol) of triethylamine in 40 ml of methylene chloride was added 985 mg (4.96 mmol) under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 960 mg of the desired compound (free base) (70.0%, colorless powder), mp: 124.0-125.0°C.

Anal. for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S,

Calcd.: C; 62.48, H; 5.59, N; 9.71

Found: C; 62.59, H; 5.77, N; 9.41

NMR (200 MHz, CDCl<sub>3</sub>) δ: 2.06 (2H, quint., J=7Hz), 3.07 (2H, t, J=7Hz), 3.63 (2H, q, J=7Hz), 6.84 (1H, td, J=8, 1Hz), 6.88 (1H, m), 6.99 (1H, dd, J=8, 1Hz), 7.10 (2H, dd, J=5, 2Hz), 7.39 (1H, td, J=9, 1Hz), 7.41 (1H, dd, J=8, 1Hz), 8.38 (2H, d, J=5Hz)

IR (KBr)cm<sup>-1</sup>: 3250, 3050, 1640, 1590

The above free base (400 mg, 1.39 mmol) was treated with 2N hydrogen chloride solution in methanol (5 ml, 10.0 mmol). The solvent was distilled off. The powder was washed with acetone and dried to obtain 420 mg of the desired compound (93.2%, colorless powder), mp: 74.0-76.0°C.

Anal. for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub>OSCl·1.0H<sub>2</sub>O,

Calcd.: C; 52.55, H; 5.59, N; 8.17

Found: C; 52.42, H; 5.58, N; 8.05

Example 37

## Synthesis of 4-[3-(3,5-di-t-butyl-4-hydroxybenzoylamino)propylthio]pyridine

To a solution of 1.49 g (5.94 mmol) of 3,5-di-t-butyl-4-hydroxybenzoic acid and 889 mg (7.73 mmol) of N-hydroxysuccinimide in 60 ml of methylene chloride was added 1.38 g (7.13 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. Further 1.00 g (5.94 mmol) of 4-(3-aminopropylthio)pyridine was added and the mixture was stirred at room temperature for 8 hours. The reaction mixture was washed with water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 650 mg of the desired compound (27.3%, colorless powder), mp: 203.0-204.0°C.

Anal. for  $C_{23}H_{32}N_2O_2S$ .

Calcd.: C; 68.96, H; 8.05, N; 6.99

Found: C; 68.70, H; 8.09, N; 6.80

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.46 (18H, s), 2.04 (2H, quint., J=7Hz), 3.08 (2H, t, J=7Hz), 3.57 (2H, q, J=7Hz), 7.12 (2H, dd, J=5, 2Hz), 7.65 (2H, s), 8.37 (2H, dd, J=5, 2Hz)

IR (KBr)  $cm^{-1}$ : 3270, 3070, 2950, 1620, 1590

Example 38

## Synthesis of 4-[3-(2-carboxybenzoylamino)propylthio]pyridine

A solution of 340 mg (2.02 mmol) of 4-(3-aminopropylthio)pyridine and 738 mg (4.98 mmol) of anhydrous phthalic acid in 5 ml of methylene chloride was stirred at room temperature for 30 minutes. The resulting crystals were filtered and dried to obtain 590 mg of the desired compound (92.3%, colorless powder), mp: 151.0-153.3°C.

Anal. for  $C_{16}H_{16}N_2O_3S \cdot 0.5H_2O$ .

Calcd.: C; 59.06, H; 5.27, N; 8.85

Found: C; 58.77, H; 5.09, N; 8.45

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.87 (2H, quint., J=7Hz), 3.15 (2H, t, J=7Hz), 3.35 (2H, q, J=7Hz), 7.29 (2H, dd, J=5, 2Hz), 7.42 (1H, dd, J=7, 1Hz), 7.54 (2H, td, J=7, 1Hz), 7.78 (1H, dd, J=7, 1Hz), 8.37 (2H, d, J=5Hz)

IR (Neat)  $cm^{-1}$ : 3250, 3080, 2950, 1700, 1640, 1590

Example 39

## Synthesis of 4-[3-(4-phenyl-n-butyrylamino)propylthio]pyridine

To a suspension of 3.28 g (20.0 mmol) of 4-phenylbutyric acid in 100 ml of benzene was added 6.98 ml (80.0 mmol) of oxalyl chloride and the mixture was refluxed for 1 hour. After cooling, the solvent was distilled off to obtain 3.60 g of the desired compound (98.5 %). To a solution of 2.00 g (8.29 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 4.16 ml (29.8 mmol) of triethylamine in 90 ml of methylene chloride was added 1.80 g (10.0 mmol) of 4-phenyl-n-butyryl chloride under ice-cooling with stirring and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain 2.25 g of the desired compound (86.3%, colorless powder), mp: 58.0-59.0°C.

Anal. for  $C_{18}H_{22}N_2OS$ .

Calcd.: C; 68.75, H; 7.05, N; 8.91, S; 10.20

Found: C; 68.95, H; 7.13, N; 8.89, S; 10.17

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.91 (2H, quint., J=7Hz), 1.97 (2H, quint., J=7Hz), 2.18 (2H, t, J=7Hz), 2.66 (2H, t, J=7Hz), 2.99 (2H, t, J=7Hz), 3.40 (2H, q, J=7Hz), 5.66 (1H, m), 7.08 (2H, dd, J=5, 2Hz), 7.10-7.35 (5H, m), 8.37 (2H, dd, J=5, 2Hz)

IR (KBr)  $cm^{-1}$ : 3320, 2940, 1640, 1580



Example 40

## Synthesis of 4-[3-(benzoylamino)propylthio]pyridine

5 To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.77 ml (19.8 mmol) of triethylamine in 40 ml of methylene chloride was added 0.58 ml (4.96 mmol) of benzoyl chloride under ice-cooling with stirring and the mixture stirred at room temperature for 30 minutes. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution and water and dried. The solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 960 mg of the desired  
 10 compound (84.9%, colorless needles). mp: 120.0-121.0°C.

Anal. for  $C_{15}H_{16}N_2OS$ .

Calcd.: C; 66.15, H; 5.92, N; 10.29

Found: C; 66.12, H; 5.95, N; 10.18

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.05 (2H, quint., J=7Hz), 3.07 (2H, t, J=7Hz), 3.62 (2H, q, J=7Hz), 6.65 (1H, m), 7.10 (2H, dd, J=5, 2Hz), 7.35-7.60 (3H, m), 7.70-7.85 (2H, m), 8.37 (2H, dd, J=5, 2Hz)  
 15

IR (KBr)  $cm^{-1}$ : 3300, 1620, 1580

Example 41

## 20 Synthesis of 4-[3-(nicotinoylamino)propylthio] pyridine

To a solution of 10.0 g (41.5 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 27.7 ml (200 mmol) of triethylamine in methylene chloride (100 ml), 8.86 g (49.8 mmol) of nicotinoyl chloride hydrochloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction  
 25 mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain powder. The powder was washed with ether and dried to obtain the desired compound (8.50 g, yield: 75.8%, pale yellow powder).

mp: 90.0-91.0°C.

30 Anal. for  $C_{14}H_{15}N_3OS$ .

Calcd.: C; 61.51, H; 5.53, N; 15.37

Found: C; 61.31, H; 5.61, N; 15.27

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.08 (2H, quint., J=7Hz), 3.08 (2H, t, J=7Hz), 3.65 (2H, q, J=7Hz), 6.84 (1H, m), 7.10 (2H, dd, J=5, 2Hz), 7.40 (1H, dd, J=8, 5Hz), 8.13 (1H, dt, J=8, 2Hz), 8.37 (2H, dd, J=5, 2Hz), 8.73 (1H, dd, J=5, 2Hz), 8.99 (1H, d, J=2Hz).  
 35

IR (KBr)  $cm^{-1}$ : 3320, 3030, 1630.

Example 42

## 40 Synthesis of 4-[3-(2-picolynoylamino)propylthio] pyridine

To a solution of 20.0 g (82.9 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 55.5 ml (400 mmol) of triethylamine in 200 ml of methylene chloride, 17.8 g (100 mmol) of 2-picolynoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was  
 45 washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain powder. The powder was recrystallized from hexane/ethyl acetate (=1:1) to obtain the desired compound (18.8 g, yield: 82.9%, pale yellow needles).

mp: 52.0-53.0°C

50 Anal. for  $C_{14}H_{15}N_3OS$ .

Calcd.: C; 61.51, H; 5.53, N; 15.37, S; 11.73

Found: C; 61.46, H; 5.48, N; 15.30, S; 11.83

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.07 (2H, quint., J=7Hz), 3.08 (2H, t, J=7Hz), 3.65 (2H, q, J=7Hz), 7.12 (2H, dd, J=5, 2Hz), 7.45 (1H, ddd, J=8, 5, 1Hz), 7.87 (1H, td, J=8, 2Hz), 8.20 (2H, dt, J=8, 1Hz), 8.38 (2H, dd, J=5, 2Hz),  
 55 8.55 (1H, ddd, J=5, 2, 1Hz).

IR (KBr)  $cm^{-1}$ : 3350, 3050, 2940, 1660.

Example 43

## Synthesis of 4-[3-(4-picolynoylamino)propylthio]pyridine

5 To a solution of 20.0 g (82.9 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 55.5 ml (400 mmol) of triethylamine in 200 ml of methylene chloride, 17.7 g (9.95 mmol) of 4-picolynoyl chloride hydrochloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:5) to obtain powder. The powder was washed with ether and dried to obtain the desired compound (1.63 g, yield: 71.9%, pale brown powder).

mp: 115.0-117.0°C

Anal. for  $C_{14}H_{15}N_3OS \cdot 0.3H_2O$ .

Calcd.: C; 60.32, H; 5.64, N; 15.07

15 Found: C; 60.62, H; 5.58, N; 14.81.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.07 (2H, quint., J=7Hz), 3.07 (2H, t, J=7Hz), 3.64 (2H, q, J=7Hz), 6.92 (1H, m), 7.09 (2H, dd, J=5.2Hz), 7.62 (1H, dd, J=5.2Hz), 8.36 (1H, dd, J=5.2Hz), 8.73 (2H, dd, J=5.2Hz).

IR (KBr) $cm^{-1}$ : 3250, 3030, 2950, 1670.

20 Example 44

## Synthesis of 4-[3-(3-quinolineacryloylamino) propylthio]pyridine

To a solution of 396 mg (1.64 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 0.27 ml (1.97 mmol) of triethylamine in 20 ml of methylene chloride, 500 mg (1.96 mmol) of 3-quinolineacryloyl chloride hydrochloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain powder. The powder was washed with ether and dried to obtain the desired compound (480 mg, yield: 83.8%, pale yellow powder).

mp: 154.0-155.0°C

Anal. for  $C_{20}H_{19}N_3OS$ ,

Calcd.: C; 68.74, H; 5.48, N; 12.02

Found: C; 68.50, H; 5.48, N; 11.84

35 NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.04 (2H, quint., J=7Hz), 3.07 (2H, t, J=7Hz), 3.60 (2H, q, J=7Hz), 6.50 (1H, t, J=6Hz), 6.66 (1H, d, J=16Hz), 7.10 (2H, dd, J=5.2Hz), 7.56 (1H, td, J=8.1Hz), 7.73 (1H, td, J=8.1Hz), 7.80 (1H, d, J=16Hz), 7.81 (1H, d, J=8Hz), 8.07 (1H, d, J=8Hz), 8.16 (1H, d, J=2Hz), 8.38 (2H, dd, J=5.2Hz), 9.06 (1H, d, J=2Hz).

IR (KBr) $cm^{-1}$ : 3300, 3030, 1650, 1620.

40

Example 45

## Synthesis of 4-[3-(1-methyl-2-pyrrolecarbonyl amino)propylthio]pyridine

45 Oxalyl chloride [3.49 ml (40 mmol)] was added to a suspension of 1.25 g (10.0 mmol) of 1-methyl-2-pyrrolecarboxylic acid in 50 ml of benzene, and the mixture was refluxed for 1 hour. After cooling, the solvent was distilled off to obtain the desired compound (1.80 g, yield: 98.5%). To a solution of 2.00 g (8.29 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 4.16 ml (29.8 mmol) of triethylamine in 90 ml of methylene chloride, 1.45 g (10.0 mmol) of the above acid chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain 1.97 g of the desired compound (yield: 86.3%, colorless powder).

mp: 74.0-75.0°C

55 Anal. for  $C_{14}H_{17}N_3OS$ ,

Calcd.: C; 61.06, H; 6.22, N; 15.26

Found: C; 60.99, H; 6.30, N; 15.14.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.01 (2H, quint., J=7Hz), 3.06 (2H, t, J=7Hz), 3.53 (2H q, J=7Hz), 3.94 (3H,

s), 6.08 (1H, dd, J=4.2Hz), 6.55 (1H, m), 6.53 (1H, dd, J=4.2Hz), 6.73 (1H, t, J=2Hz), 7.11 (2H, dd, J=5.2Hz), 8.39 (2H, dd, J=5.2Hz).

IR (KBr)cm<sup>-1</sup>: 3270, 2940, 1650.

#### 5 Example 46

##### Synthesis of 4-[3-(2-thenoylamino)propylthio]pyridine

To a solution of 10.0 g (41.5 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 27.7 ml (200 mmol) of triethylamine in 100 ml of methylene chloride, 5.35 ml (50.0 mmol) of 2-thenoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:20) to obtain powder. The powder was recrystallized from methanol/ethyl acetate (=1:20) to obtain 8.05 g of the desired compound (yield: 70.5%, yellow prisms).

mp: 112.0-113.0°C

Anal. for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>OS<sub>2</sub>.

Calcd.: C; 56.09, H; 5.07, N; 10.06, S; 23.04

Found: C; 56.17, H; 5.10, N; 10.00, S; 23.22.

<sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>) δ: 2.04 (2H, quint., J=7Hz), 3.07 (2H, t, J=7Hz), 3.59 (2H, q, J=7Hz), 6.44 (1H, m), 7.08 (1H, dd, J=5.4Hz), 7.11 (2H, dd, J=5.2Hz), 7.48 (1H, dd, J=5.1Hz), 7.52 (1H, dd, J=4.1Hz), 8.38 (2H, dd, J=5.2Hz).

IR (KBr)cm<sup>-1</sup>: 3210, 3040, 1640.

#### 25 Example 47

##### Synthesis of 2-[3-(thenoylamino)propylthio]pyridine

To a solution of 1.50 g (6.22 mmol) of 2-(3-aminopropylthio)pyridine dihydrochloride and 3.19 ml (22.9 mmol) of triethylamine in 60 ml of methylene chloride, 1.09 ml (7.46 mmol) of 2-thenoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain powder. The powder was washed with ether and dried to obtain 1.48 g of the desired compound (yield: 85.5%, colorless powder).

mp: 81.0-82.0°C

Anal. for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>OS<sub>2</sub>.

Calcd.: C; 56.09, H; 5.07, N; 10.06

Found: C; 55.51, H; 5.00, N; 9.61.

<sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>) δ: 2.00 (2H, quint., J=7Hz), 3.33 (2H, t, J=7Hz), 3.56 (2H, q, J=7Hz), 7.01 (1H, dd, J=7.5, 1Hz), 7.11 (1H, dd, J=5.4Hz), 7.23 (1H, dt, J=8.1Hz), 7.35-7.55 (3H, m), 7.61 (1H, dd, J=4.1Hz), 8.45 (1H, ddd, J=5.2, 1Hz)

IR (KBr)cm<sup>-1</sup>: 3350, 3070, 2920, 1620.

#### 45 Example 48

##### Synthesis of 3-[3-(thenoylamino)propylthio]pyridine

##### i) 3-(3-Aminopropylthio)pyridine dihydrochloride

A solution of 2.00 g (11.0 mmol) of 3-(dimethylaminocarbonylthio)pyridine in 2 ml of methanol was added to 40 ml (80.0 mmol) of a 2N aqueous solution of sodium hydroxide, and the mixture was heated with stirring at 60°C for 30 minutes. After cooling, 2.40 g (11.0 mmol) of 3-bromopropylamine hydrobromide was added and the resulting mixture was further stirred for 30 minutes. After cooling, the reaction mixture was extracted with ethyl acetate. The extract was separated and dried, and then the solvent was distilled off. The residue was treated with 15 ml (30.0 mmol) of a 2N solution of hydrogen chloride in methanol. The solvent was distilled off to obtain powder. The powder was washed with acetone and dried to obtain the desired compound (2.62 g, yield: 98.8%).

mp: 169.0-171.0°C.

Anal. for  $C_8H_{14}N_2SCl_2$ .

Calcd.: C; 37.07, H; 6.22, N; 10.81

Found: C; 36.88, H; 5.62, N; 10.66.

5 NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.08 (2H, quint., J=7Hz), 3.17 (2H, t, J=7Hz), 3.28 (2H, t, J=7Hz), 7.98 (1H, dd, J=8.6Hz), 8.55 (1H, d, J=8Hz), 8.59 (1H, d, J=6Hz), 8.73 (1H, s).  
IR (KBr) $cm^{-1}$ : 2930, 1610, 1520.

## ii) Synthesis of 3-[3-(thenoylamino)propylthio]pyridine

10

To a solution of 2.00 g (8.29 mmol) of 3-(3-aminopropylthio)pyridine dihydrochloride and 4.16 ml (29.9 mmol) of triethylamine in 80 ml of methylene chloride, 1.06 ml (9.95 mmol) of 2-thenoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain powder. The powder was washed with ether and dried to obtain 1.97 g of the desired compound (yield: 85.3%, yellow powder).

mp: 66.0-67.0°C

Anal. for  $C_{13}H_{14}N_2OS_2$ .

20 Calcd.: C; 56.09 H; 5.07, N; 10.06

Found: C; 55.90 H; 5.06, N; 9.94.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 1.95 (2H, quint., J=7Hz), 3.01 (2H, t, J=7Hz), 3.57 (2H, q, J=7Hz), 6.36 (1H, m), 6.67 (1H, dd, J=5.4Hz), 7.22 (1H, ddd, J=8.5, 0.6Hz), 7.47 (1H, dd, J=5.1Hz), 7.50 (1H, dd, J=4.1Hz), 7.67 (1H, ddd, J=8.2, 1Hz), 8.43 (1H, dd, J=5.1Hz), 8.58 (1H, dd, J=2.0, 0.6Hz).

25 IR (KBr) $cm^{-1}$ : 3340, 3060, 2930, 1620.

## Example 49

### Synthesis of 4-[3-(thenoylamino)propylsulfinyl]pyridine

30

To a solution of 1.00 g (3.52 mmol) of 4-[3-(t-butoxycarbonylamino)propylsulfinyl]pyridine in 2 ml of methanol, 20 ml (40.0 mmol) of a 2N solution of hydrogen chloride in methanol was added. The mixture was stirred for 1 hour at room temperature. The solvent was distilled off. To 900 mg of the residue (Anal. calcd. for  $C_8H_{14}N_2O_2SCl_2 \cdot 0.5H_2O$ : C; 36.10, H; 5.68, N; 10.52. Found C; 35.92, H; 5.95, N; 10.44.) thus obtained and 1.59 ml (11.4 mmol) of triethylamine in 30 ml of methylene chloride, 0.41 ml (3.79 mmol) of 2-thenoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain powder. The powder was washed with ether and dried to obtain 740 mg of the desired compound (yield: 71.5%, colorless powder).

mp: 101.0-102.0°C

Anal. for  $C_{13}H_{14}N_2O_2S_2$ .

Calcd.: C; 53.04, H; 4.79, N; 9.52

Found: C; 52.96, H; 4.76, N; 9.49.

45 NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.99 (1H, dq, J=14.7Hz), 2.15 (1H, dq, J=14.7Hz), 2.90 (1H, dt, J=14.7Hz), 3.13 (1H, dt, J=14.7Hz), 3.58 (1H, q, J=7Hz), 3.59 (1H, q, J=7Hz), 6.20 (1H, m), 7.04 (1H, dd, J=5.4Hz), 7.49 (1H, dd, J=5.1Hz), 7.54 (2H, dd, J=5.2Hz), 7.58 (1H, dd, J=4.1Hz), 8.78 (1H, dd, J=5.2Hz).

IR (KBr) $cm^{-1}$ : 3370, 3320, 1630.

## Example 50

### Synthesis of 4-[3-(thenoylamino)propylsulfonyl]pyridine

55 To a solution of 1.00 g (3.33 mmol) of 4-[3-(t-butoxycarbonylamino)propylsulfonyl]pyridine in 2 ml of methanol, 20 ml (20.0 mmol) of a 2N solution of hydrogen chloride in methanol was added. The mixture was stirred for 1 hour at room temperature. The solvent was distilled off. To 920 mg of the residue (Anal. calcd. for  $C_8H_{14}N_2O_2SCl_2 \cdot 0.3H_2O$ : C; 34.48, H; 5.28, N; 10.06. Found C; 34.58, H; 5.46, N; 9.92.) thus obtained and 1.47 ml (10.5 mmol) of triethylamine in 30 ml of methylene chloride, 0.38 ml (3.51 mmol) of 2-thenoyl chloride was

added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain powder. The powder was washed with ether and dried to obtain 757 mg of the desired compound (yield: 72.6%, colorless powder).

mp: 124.0-125.0°C

Anal. for  $C_{13}H_{14}N_2O_3S_2$ .

Calcd.: C; 50.30, H; 4.55, N; 9.03

Found: C; 50.31, H; 4.55, N; 8.99.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.12 (2H, quint., J=7Hz), 3.25 (2H, t, J=7Hz), 3.60 (2H, q, J=7Hz), 6.54 (1H, m), 7.08 (1H, dd, J=5.4Hz), 7.49 (1H, dd, J=5.1Hz), 7.52 (1H, dd, J=4.1Hz), 7.77 (1H, dd, J=5.2Hz), 8.92 (1H, dd, J=5.2Hz).

IR (KBr) $cm^{-1}$ : 3380, 3080, 1630.

#### Example 51

Synthesis of 4-3-(N-methyl-2-thenoylamino)propylthio)pyridine

##### i) Synthesis of 4-(3-hydroxypropylthio)pyridine

In 100 ml of methylene chloride were dissolved 11.1 g (100 mmol) of 4-mercaptopyridine and 13.9 ml (100 mmol) of triethylamine, and 9.04 ml (100 mmol) of 3-bromo-1-propanol was added. The mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with a 1N aqueous solution of sodium hydroxide and water and dried. Then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 14.2 g of the desired compound (yield: 83.9%, yellow oil).

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 1.97 (2H, quint., J=7Hz), 3.12 (2H, t, J=7Hz), 3.81 (2H, t, J=7Hz), 7.14 (2H, dd, J=5.2Hz), 8.37 (2H, dd, J=5.2Hz).

IR (neat) $cm^{-1}$ : 3350, 2940, 1580.

##### ii) Synthesis of 4-[3-(N-methyl-2-thenoylamino)propylthio)pyridine

To a solution of 3.46 g (20.4 mmol) of 4-(3-hydroxypropylthio)pyridine and 3.42 ml (24.5 mmol) of triethylamine in 100 ml of methylene chloride, 1.90 ml (24.5 mmol) of methanesulfonyl chloride was added. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried. Then the solvent was distilled off.

To 10 ml of a solution of 2.00 g of the obtained residue (4.00 g) in methanol, 3.14 g (40.5 mmol) of a 40% solution of methylamine in methanol was added. The resulting mixture was heated at 80°C for 1 hour in a sealed tube. After cooling, the solvent was distilled off. To a solution of 1.52 g of the residue thus obtained and 1.35 ml (9.71 mmol) in triethylamine in 80 ml of methylene chloride, 1.34 ml (9.71 mmol) of 2-thenoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried. Then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain powder. The powder was washed with ether and dried to obtain 1.62 g of the desired compound (yield: 68.5%, pale yellow powder).

mp: 72.0-72.5°C.

Anal. for  $C_{14}H_{16}N_2OS_2$ .

Calcd.: C; 57.50, H; 5.51, N; 9.58

Found: C; 57.44, H; 5.56, N; 9.60.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.07 (2H, quint., J=7Hz), 3.02 (2H, t, J=7Hz), 3.21 (3H, s), 3.69 (2H, t, J=7Hz), 7.05 (1H, dd, J=5.4Hz), 7.10 (2H, dd, J=5.2Hz), 7.36 (1H, d, J=4Hz), 7.46 (1H, dd, J=5.1Hz), 8.40 (2H, dd, J=5.2Hz).

IR (KBr) $cm^{-1}$ : 3100, 2930, 1590.

#### Example 52

Synthesis of 4-[3-(N-phenyl-2-thenoylamino)propylthio)pyridine

To a solution of 1.50 g (8.86 mmol) of 4-(3-hydroxypropylthio)pyridine and 1.48 ml (10.6 mmol) of triethy-

amine in 90 ml of methylene chloride, 0.82 ml (10.6 mmol) of methanesulfonyl chloride was added. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. 1.94 g (17.7 mmol) of aniline was added to 1.70 g of the residue and the mixture was heated at 80°C for 1 hour. After cooling, the mixture was purified by column chromatography (eluent: ethyl acetate) to obtain yellow oil (680 mg, yield: 31.4%). To a solution of 350 mg (1.43 mmol) of the oil and 0.24 ml (1.72 mmol) of triethylamine in 15 ml of methylene chloride, 0.18 ml (1.72 mmol) of 2-thenoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain powder. The powder was washed with ether and dried to obtain 413 mg of the desired compound (yield: 81.5%, pale yellow powder).

mp: 66.0-67.0°C

Anal. for  $C_{19}H_{18}N_2OS_2 \cdot 0.2H_2O$

Calcd.: C; 63.73, H; 5.18, N; 7.82

Found: C; 63.82, H; 5.11, N; 7.77.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.07 (2H, quint., J=7Hz), 3.05 (2H, t, J=7Hz), 4.02 (2H, t, J=7Hz), 6.69 (1H, dd, J=4.1Hz), 6.78 (1H, dd, J=5.4Hz), 7.07 (2H, dd, J=5.2Hz), 7.15-7.30 (2H, m), 7.31 (1H, dd, J=5.1Hz), 7.35-7.50 (3H, m), 8.36 (2H, dd, J=5.2Hz).

IR (KBr) $cm^{-1}$ : 3430, 3090, 3020, 1580.

#### Example 53

##### Synthesis of 4-[3-(2-furoylamino)propylthio]pyridine

To a solution of 1.00 g (4.15 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.78 ml (19.9 mmol) of triethylamine in 40 ml of methylene chloride, 0.49 ml (4.98 mmol) of 2-furoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain powder. The powder was washed with ether and dried to obtain 950 mg of the desired compound (yield: 87.3%, colorless powder).

mp: 98.0-99.0°C.

Anal. for  $C_{13}H_{14}N_2O_2S$ .

Calcd.: C; 59.52, H; 5.38, N; 10.68

Found: C; 59.30, H; 5.39, N; 10.45.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.03 (2H, quint., J=7Hz), 3.07 (2H, t, J=7Hz), 3.59 (2H, q, J=7Hz), 6.51 (1H, dd, J=4.2Hz), 6.55 (1H, m), 7.00-7.20 (3H, m), 7.44 (1H, d, J=2Hz), 8.40 (2H, dd, J=5.2Hz).

IR (KBr) $cm^{-1}$ : 3360, 3030, 2920, 1630.

#### Example 54

##### Synthesis of 4-[3-(3-thiophenecarbonylamino)propylthio]pyridine

To a solution of 1.00 g (7.80 mmol) of thiophene-3-carboxylic acid and 1.08 g (10.1 mmol) of N-hydroxy-succinimide in 70 ml of methylene chloride, 1.80 g (9.36 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 1 hour. Further, 1.31 g (7.80 mmol) of 4-(3-aminopropylthio)pyridine was added, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain 1.65 g of the desired compound (yield: 76.1%, colorless powder).

mp: 121.0-122.0°C.

Anal. for  $C_{13}H_{14}N_2OS_2$ .

Calcd.: C; 56.09, H; 5.07, N; 10.06

Found: C; 56.07, H; 4.99, N; 10.23.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.04 (2H, quint., J=7Hz), 3.06 (2H, t, J=7Hz), 3.58 (2H, q, J=7Hz), 6.45 (1H, m), 7.10 (2H, dd, J=5.2Hz), 7.34 (1H, ddd, J=5.3, 0.8Hz), 7.39 (1H, dd, J=5.1Hz), 7.88 (1H, dd, J=3.1Hz), 8.37 (2H, dd, J=5.2Hz).

IR (KBr) $cm^{-1}$ : 3340, 1630.

Example 55

## Synthesis of 4-[3-(2-thienylacetyl-amino)propylthio]pyridine

To a solution of 913 mg (6.42 mmol) of 2-thienylacetic acid and 961 mg (8.35 mmol) of N-hydroxysuccinimide in 65 ml of methylene chloride, 1.48 g (7.70 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 1 hour. Further, 1.08 g (6.42 mmol) of 4-(3-aminopropylthio)pyridine was added, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: methanol/ethyl acetate=1:10) to obtain powder. The powder thus obtained was washed with ether and dried to obtain 1.62 g of the desired compound (yield: 86.3%, pale yellow powder).

mp: 62.0-63.0°C.

Anal. for  $C_{14}H_{16}N_2OS_2 \cdot 0.1H_2O$ .

Calcd.: C; 57.15, H; 5.55, N; 9.52

Found: C; 57.06, H; 5.53, N; 9.44.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 1.89 (2H, quint., J=7Hz), 2.94 (2H, t, J=7Hz), 3.39 (2H, q, J=7Hz), 3.79 (2H, s), 5.84 (1H, m), 6.94 (1H, bd, J=3Hz), 7.00 (1H, dd, J=5.3Hz), 7.05 (2H, dd, J=5.2Hz), 7.26 (1H, dd, J=5.1Hz), 7.88 (1H, dd, J=3.1Hz), 8.38 (2H, dd, J=5.2Hz).

IR (KBr)cm<sup>-1</sup>: 3230, 3040, 1660, 1590.

Example 56

## Synthesis of 4-[3-(2-thiopheneacrylamino)propylthio]pyridine

To a solution of 1.37 g (8.91 mmol) of 2-thiopheneacrylic acid and 1.33 g (11.6 mmol) of N-hydroxysuccinimide in 90 ml of methylene chloride, 2.05 g (10.7 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 1 hour. Further, 1.50 g (8.91 mmol) of 4-(3-aminopropylthio)pyridine was added, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was washed and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain powder. The powder thus obtained was washed with ether and dried to obtain 1.95 g of the desired compound (yield: 71.9%, colorless powder).

mp: 111.0-112.0°C.

Anal. for  $C_{15}H_{16}N_2OS_2$ .

Calcd.: C; 59.18, H; 5.30, N; 9.20

Found: C; 59.26, H; 5.36, N; 9.15.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.00 (2H, quint., J=7Hz), 3.04 (2H, t, J=7Hz), 3.54 (2H, q, J=7Hz), 6.05 (1H, m), 6.21 (1H, d, J=15Hz), 7.03 (1H, dd, J=5.3Hz), 7.10 (2H, dd, J=5.2Hz), 7.21 (1H, d, J=3Hz), 7.31 (1H, d, J=5Hz), 7.76 (1H, d, J=15Hz), 8.38 (2H, dd, J=5.2Hz).

IR (KBr)cm<sup>-1</sup>: 3290, 3070, 1640, 1600.

Example 57

## Synthesis of 4-[3-(thianaphene-2-carbonylamino)propylthio]pyridine

To a solution of 2.00 g (8.29 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 4.17 ml (29.9 mmol) of triethylamine in 80 ml of methylene chloride, 1.96 ml (9.95 mmol) of thianaphene-2-carbonyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain powder. The powder thus obtained was washed with ether and dried to obtain 2.40 g of the desired compound (yield: 97.6%, pale yellow powder).

mp: 123.0-124.0°C.

Anal. for  $C_{17}H_{16}N_2OS_2$ .

Calcd.: C; 62.17, H; 4.91, N; 8.53

Found: C; 61.97, H; 4.89, N; 8.42.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.07 (2H, quint., J=7Hz), 3.07 (2H, t, J=7Hz), 3.63 (2H, q, J=7Hz), 6.66 (1H,

m), 7.10 (1H, dd, J=5.2Hz), 7.30-7.50 (2H, m), 7.75-7.90 (3H, m), 8.37 (2H, dd, J=5.2Hz).  
IR (KBr)cm<sup>-1</sup>: 3330, 3030, 2930, 1620.

#### Example 58

##### Synthesis of 4-[3-(4,5-dibromothiophenylamino)propylthio]pyridine

To a solution of 2.55 g (8.91 mmol) of 4,5-dibromothiophene-2-carboxylic acid and 1.33 g (11.6 mmol) of N-hydroxysuccinimide in 90 ml of methylene chloride, 2.05 g (10.7 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 1 hour. Further, 1.50 g (8.91 mmol) of 4-(3-aminopropylthio)pyridine was added, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain powder. The powder thus obtained was washed with ether and dried to obtain 2.79 g of the desired compound (yield: 71.8%, colorless powder).

mp: 129.0-130.0°C.

Anal. for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>OBr<sub>2</sub>S<sub>2</sub>.

Calcd.: C; 35.80, H; 2.77, N; 6.42

Found: C; 35.52, H; 2.70, N; 6.23.

NMR (200MHz, CDCl<sub>3</sub>) δ: 2.02 (2H, quint., J=7Hz), 3.04 (2H, t, J=7Hz), 3.57 (2H, q, J=7Hz), 6.64 (1H, t, J=6Hz), 7.08 (2H, dd, J=5.2Hz), 7.29 (1H, s), 8.37 (2H, dd, J=5.2Hz).

IR (KBr)cm<sup>-1</sup>: 3200, 3080, 3020, 1640, 1580.

#### Example 59

##### Synthesis of 4-[3-(5-methylthiophenylamino)propylthio]pyridine

To a solution of 1.27 g (8.91 mmol) of 5-methyl-2-thiophenecarboxylic acid and 1.33 g (11.6 mmol) of N-hydroxysuccinimide in 90 ml of methylene chloride, 2.05 g (10.7 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 1 hour. Further, 1.50 g (8.91 mmol) of 4-(3-aminopropylthio)pyridine was added, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain powder. The powder thus obtained was washed with ether and dried to obtain 1.68 g of the desired compound (yield: 64.5%, colorless powder).

mp: 86.0-87.0°C.

Anal. for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>OS<sub>2</sub>.

Calcd.: C; 57.50, H; 5.51, N; 9.58

Found: C; 57.35, H; 5.51, N; 9.49.

NMR (200MHz, CDCl<sub>3</sub>) δ: 2.02 (2H, quint., J=7Hz), 2.51 (3H, d, J=1Hz), 3.05 (2H, t, J=7Hz), 3.57 (2H, q, J=7Hz), 6.25 (1H, t, J=5Hz), 6.73 (1H, dd, J=4.1Hz), 7.10 (2H, dd, J=5.2Hz), 7.32 (1H, d, J=4Hz), 8.38 (2H, dd, J=5.2Hz).

IR (KBr)cm<sup>-1</sup>: 3320, 3030, 2940, 1610.

#### Example 60

##### Synthesis of 4-[3-(3-methylthiophenylamino)propylthio]pyridine

In 100 ml of benzene was suspended 3.00 g (21.1 mmol) of 3-methyl-2-thiophenecarboxylic acid, oxalyl chloride [7.36 ml (84.4 mmol)] was added and the mixture was refluxed for 2 hours. After cooling, the solvent was distilled off to obtain 3.40 g of 3-methylthiophenyl chloride (yield: quant.). To a solution of 1.50 g (6.23 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 2.61 ml (18.7 mmol) of triethylamine in 60 ml of methylene chloride, 1.20 ml (7.48 mmol) of the 3-methylthiophenyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain powder. The powder was washed with ether and dried to obtain 1.54 g of the desired compound (yield: 84.5%, pale yellow powder).

mp: 104.0-105.0°C



Anal. for  $C_{14}H_{16}N_2O_2S_2$ .

Calcd.: C; 57.50, H; 5.51, N; 9.58

Found: C; 57.23, H; 5.50, N; 9.52.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.04 (2H, quint.,  $J=7$ Hz), 2.52 (3H, s), 3.07 (2H, t,  $J=7$ Hz), 3.57 (2H, q,  $J=7$ Hz),  
 5 6.60 (1H, m), 6.89 (1H, d,  $J=5$ Hz), 7.11 (1H, dd,  $J=5,2$ Hz), 7.26 (1H, d,  $J=5$ Hz), 8.38 (2H, dd,  $J=5,2$ Hz).  
 IR (KBr) $cm^{-1}$ : 3220, 3090, 3040, 1630.

#### Example 61

##### 10 Synthesis of 2-[3-(2-thenoylamino)propyloxy]pyridine

In 50 ml of DMF was suspended 3.04 g (76 mmol) of 60% oily sodium hydride, a mixture of 10.0 g (63.5 mmol) of 2-bromopyridine and 4.47 mmol (63.5 mmol) of 3 amino-1-propanol was added dropwise under ice-cooling with stirring. The mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted  
 15 with chloroform, washed with water and dried. Then the solvent was distilled off. The residue was purified by column chromatography (eluent: conc. ammonia water/methanol=1:50) to obtain 2.00 g of pale yellow oil (yield: 20.7%). To a solution of the above oil and 2.20 ml (15.8 mmol) of triethylamine in 50 ml of methylene chloride, 1.69 ml (15.8 mmol) of 2-thenoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of  
 20 sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: hexane/ethyl acetate=1:1) to obtain powder. The powder was washed with ether and dried to obtain 2.20 g of the desired compound (yield: 63.8%, colorless powder).

mp: 91.0-92.0°C

Anal. for  $C_{13}H_{14}N_2O_2S$ .

25 Calcd.: C; 59.52, H; 5.38, N; 10.68

Found: C; 59.14, H; 5.14, N; 10.45.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.07 (2H, quint.,  $J=7$ Hz), 3.59 (2H, q,  $J=7$ Hz), 4.50 (2H, t,  $J=7$ Hz), 6.77 (1H, d,  $J=8$ Hz), 6.90 (1H, td,  $J=5,1$ Hz), 7.03 (1H, m), 7.10 (1H, dd,  $J=5,4$ Hz), 7.47 (1H, td,  $J=5,1$ Hz), 7.56 (1H, dd,  $J=4,1$ Hz), 7.61 (1H, ddd,  $J=8,5,2$ Hz), 8.18 (1H, dd,  $J=5,2$ Hz).

30 IR (KBr) $cm^{-1}$ : 3280, 3050, 2940, 1620.

#### Example 62

##### Synthesis of 4-(phthalimidomethylthio)pyridine

35 In 250 ml of ethanol were suspended 6.95 g (62.5 mmol) of 4-mercaptopyridine and 15.0 g (62.5 mmol) of (N-bromomethyl)phthalimide, triethylamine [10.5 ml (74.8 mmol)] was added and the mixture was stirred at room temperature for 18 hours. The solvent was distilled off. The residue was dissolved in chloroform, washed with a saturated aqueous solution of sodium bicarbonate and water and dried. Then the solvent was distilled  
 40 off. The residue was purified by column chromatography (eluent: chloroform/ethyl acetate=3:2) to obtain powder. The powder thus obtained was recrystallized from ethyl acetate to obtain 12.0 g of the desired compound (yield: 71.6%, colorless needles).

mp: 133.0-134.0°C

Anal. for  $C_{14}H_{10}N_2O_2S$ .

45 Calcd.: C; 62.21, H; 3.73, N; 10.36, S; 11.86

Found: C; 62.21, H; 3.73, N; 10.32, S; 11.86.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 5.19 (2H, s), 7.41 (2H, dd,  $J=5,2$ Hz), 7.70-7.80 (2H, m), 7.80-7.95 (2H, m), 8.45 (2H, dd,  $J=5,2$ Hz).

IR (KBr) $cm^{-1}$ : 1770, 1710.

#### Example 63

##### Synthesis of 3-(phthalimidomethylthio)pyridine

55 To a solution of 1.00 g (5.49 mmol) of 3-(dimethylaminocarbonylthio)pyridine in 50 ml of methanol, 5.49 ml (5.49 mmol) of a 1N aqueous solution of sodium hydroxide was added. The mixture was heated at 60°C for 1 hour with stirring. After cooling, the solvent was distilled off. The residue was dissolved in ethanol and dried. The solvent was distilled off. The residue thus obtained and 1.58 g of (6.59 mmol) of (N-bromomethyl)phtha-

limide were suspended in 50 ml of ethanol, and 0.92 ml (6.59 mmol) of triethylamine was added. The mixture was stirred at room temperature for 4 hours. The solvent was distilled off, and the residue was dissolved in chloroform, washed with water and dried. Then the solvent was distilled off. The residue was purified by column chromatography (eluent: hexane/ethyl acetate=1:1) to obtain powder. The powder thus obtained was washed with ether and dried to obtain 1.20 g of the desired compound (yield: 80.9%, colorless powder).

mp: 123.0-124.0°C

Anal. for  $C_{14}H_{10}N_2O_2S$ .

Calcd.: C; 62.21, H; 3.73, N; 10.36

Found: C; 62.62, H; 3.70, N; 9.98.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 5.04 (2H, s), 7.27 (1H, t, J=5Hz), 7.70-8.00 (5H, m), 8.52 (1H, dd, J=5,1Hz), 8.64 (1H, d, K=1Hz).

IR (KBr) $cm^{-1}$ : 1770, 1720.

#### Example 64

##### Synthesis of 2-(phthalimidomethylthio)pyridine

In 50 ml of ethanol were suspended 1.11 g (10 mmol) of 2-mercaptopyridine and 2.40 g (10.0 mmol) of (N-bromomethyl)phthalimide, triethylamine [1.54 ml (11.0 mmol)] was added and the mixture was stirred at room temperature for 4 hours. The solvent was distilled off. The residue was dissolved in chloroform, washed with water and dried. Then the solvent was distilled off. The residue was purified by column chromatography (eluent: hexane/ethyl acetate=1:1) to obtain powder. The powder thus obtained was washed with ether and dried to obtain 2.16 g of the desired compound (yield: 80.0%, colorless powder).

mp: 93.0-94.0°C

Anal. for  $C_{14}H_{10}N_2O_2S$ .

Calcd.: C; 62.21, H; 3.73, N; 10.36

Found: C; 62.07, H; 3.69, N; 10.27.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 5.54 (2H, s), 7.06 (1H, cdd, J=8,5,1Hz), 7.26 (1H, dd, J=8,1Hz), 7.53 (1H, td, J=8,1Hz), 7.65-7.75 (2H, m), 7.75-7.90 (2H, m), 8.53 (1H, dd, J=5,1Hz).

IR (KBr) $cm^{-1}$ : 1780, 1720.

#### Example 65

##### Synthesis of 4-(phthalimidomethyloxy)pyridine

To a solution of 4.76 g (50 mmol) of 4-hydroxypyridine and 10.76 g (55 mmol) of N-chloromethylphthalimide in 80 ml of DMF, 8.23 ml (55 mmol) of 1,8-diazabicyclo[5,4,0]-7-undecene was added. The mixture was stirred at room temperature for 2 hours. After the solvent was distilled off, the reaction mixture was poured into water and extracted with ethyl acetate. The precipitate was filtered off. The aqueous layer was further extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 2.67 g of the desired compound (yield: 21%, colorless crystals).

mp: 129.0-131.0°C

Anal. for  $C_{14}H_{10}N_2O_3 \cdot 0.2H_2O$ .

Calcd.: C; 65.21, H; 4.07, N; 10.86

Found: C; 65.33, H; 3.93, N; 10.66.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 5.72 (2H, s), 7.03 (1H, dd, J=5,2Hz), 7.70-7.86 (2H, m), 7.86-8.00 (2H, m), 8.47 (2H, dd, J=5,2Hz).

IR (KBr) $cm^{-1}$ : 1780, 1720, 1590.

#### Example 66

##### Synthesis of 3-(phthalimidomethyloxy)pyridine

In 100 ml of acetone were suspended 2.43 g (25.6 mmol) of 3-hydroxypyridine and 5.00 g (25.6 mmol) of (N-chloromethyl)phthalimide, potassium carbonate [3.52 g (25.6 mmol)] was added and the mixture was stirred at 60°C for 7 hours under heating. After cooling, the solvent was distilled off. The residue was dissolved in dichloromethane, washed with a saturated aqueous solution of sodium bicarbonate and water and dried. Then

the solvent was distilled off. The residue was purified by column chromatography (eluent: dichloromethane to ethyl acetate/hexane=1:1) to obtain 2.60 g of the desired compound (yield: 40.0%, colorless columns).

Anal. for  $C_{14}H_{10}N_2O_3$ .

Calcd.: C; 66.14, H; 3.96, N; 11.02

Found: C; 65.91, H; 4.17, N; 10.99.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 5.71 (2H, s), 7.27 (1H, dd,  $J=4.0, 8.6$ Hz), 7.51 (1H, ddd,  $J=1.4, 3.0, 8.6$ Hz), 7.80 (2H, dd,  $J=3.0, 5.4$ Hz), 7.94 (2H, dd,  $J=3.0, 5.4$ Hz), 8.31 (1H, dd,  $J=1.4, 4.0$ Hz), 8.44 (1H, d,  $J=3.0$ Hz).

IR (KBr)  $cm^{-1}$ : 3060, 1780, 1730, 715.

#### 10 Example 67

Synthesis of 2-(phthalimidomethoxy)pyridine

a) Method wherein a silver salt is generated in situ

15

In 4 ml of benzene were suspended 0.095 g (1.0 mmol) of 2-hydroxypyridine and 0.14 g (0.5 mmol) of silver carbonate, N-bromomethylphthalimide [0.29 g (1.2 mmol)] was added at room temperature, and the mixture was stirred at 80°C for 14 hours under heating. After cooling, the residue was filtered and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane=10:1) to obtain powder. The powder was recrystallized from ethyl acetate to obtain 0.10 g of the desired compound (yield: 39.0%, colorless columns).

20

b) Method wherein a silver salt is isolated.

25

i) Synthesis of 2-hydroxypyridine silver salt

A solution of 20.40 g (120 mmol) of silver nitrate in 200 ml of water was added to a solution of 11.42 g (120 mmol) of 2-hydroxypyridine in 300 ml of water at room temperature. The reaction mixture was neutralized with 8.0 ml of an aqueous ammonium solution. The resulting precipitate was collected, washed successively with water, ethanol and ether and dried to obtain 25.01 g of the desired compound (yield: quant., colorless columns).

30

ii) Synthesis of 2-(phthalimidomethoxy)pyridine

In 4 ml of benzene was suspended 0.20 g (1.0 mmol) of 2-hydroxypyridine silver salt, N-bromomethylphthalimide [0.29 g (1.2 mmol)] was added at room temperature, and the mixture was stirred at room temperature for 16 hours. The residue was filtered and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane=10:1) to obtain powder. The powder was recrystallized from ethyl acetate to obtain 0.21 g of the desired compound (yield: 82.5%, colorless columns).

35

Anal. for  $C_{14}H_{10}N_2O_3$ .

Calcd.: C; 66.14 H; 3.96, N; 11.02

Found: C; 65.93, H; 4.12, N; 10.96.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 6.00 (2H, s), 6.75 (1H, dt,  $J=1.0, 8.3$ Hz), 6.94 (1H, ddd,  $J=1.0, 5.2, 7.1$ Hz), 7.60 (1H, ddd,  $J=2.2, 7.0, 8.3$ Hz), 7.74-7.79 (4H, m), 8.21 (1H, ddd,  $J=1.0, 2.2, 5.2$ Hz).

IR (KBr)  $cm^{-1}$ : 3100, 3050, 1780, 1730, 1600, 1570.

45

#### Example 68

Synthesis of 4-[3-[N-(2-thienylmethyl)-N-trifluoroacetylamino]propylthio]pyridine hydrochloride

50

i) Synthesis of 4-[3-[N-(2-thienylmethyl)amino]propylthio]pyridine

In 200 ml of methylene chloride were dissolved 10.34 g (61.1 mmol) of 4-(3-hydroxypropylthio)pyridine and 10.2 ml (73.3 mmol) of triethylamine, methanesulfonyl chloride [5.7 ml (73.3 mmol)] was added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried. Then the solvent was distilled off. To 8.05 g of the residue was added 3.3 ml (32.5 mmol) of 2-thiophenemethylamine. The mixture was heated at 80°C for 3 hours. After cooling, the mixture was purified by column chromatography (eluent: chloroform/methanol=25:1) to obtain 2.5 g of the desired compound (yield: 29.1%, yellow oil).

55

ii) Synthesis of 4-[3-[N-(2-thienylmethyl)-N-trifluoroacetyl-amino]propylthio]pyridine hydrochloride

According to the same manner as that described in Example 25, the title compound was synthesized.

NMR (200MHz, DMSO- $d_6$ )  $\delta$  : 1.75-2.13 (2H, m), 3.13-3.34 (2H, m), 3.42-3.61 (2H, m), 4.80 and 4.86 (2H, each s), 6.94-7.03 (1H, m), 7.12-7.19 (1H, m), 7.50 (1H, m), 7.78-7.93 (2H, m), 8.58-8.69 (2H, m).

Example 69

Synthesis of 3-[2-(phthalimido)ethyl]-2-(pivaloylamino)pyridine

In 100 ml of ethanol was suspended 6.28 g (29.8 mmol) of 3-mercapt-2-(pivaloylamino)pyridine and 11.4 g (44.8 mmol) of N-(2-bromoethyl)phthalimide, triethylamine [8.32 m: (59.7 mmol)] was added and the mixture was heated under reflux for 1 hour. The reaction mixture was poured into water and extracted with chloroform. The combined chloroform solution was dried and then the solvent was distilled off. The residue was purified by column chromatography (eluent: hexane/ethyl acetate 1:1 to ethyl acetate) to obtain 11.0 g of the desired compound (yield: 96.3%, white solid).

NMR (200MHz,  $CDCl_3$ )  $\delta$  : 1.34 (9H, s), 3.18 (2H, t, J=6.6Hz), 3.87 (2H, t, J=6.4Hz), 7.06 (1H, dd J=4.8,7.6Hz), 7.71-7.85 (4H, m), 7.93 (1H, dd, J=1.6,7.8Hz), 8.30 (1H, dd, J=1.8,4.8Hz), 8.39 (1H, br.s).

IR (KBr) $cm^{-1}$ : 3380, 1760, 1700.

Example 70

Synthesis of 2-amino-3-[2-(phthalimido)ethyl]pyridine

Hydrochloric acid (5N) was added to 8.84 g (23.1 mmol) of 3-[2-(phthalimido)ethyl]-2-(pivaloylamino)pyridine, and the mixture was stirred at 100°C for 4 hours. After cooling, 25% ammonia water was added to the mixture to make it basic. The resulting mixture was extracted with methylene chloride. The combined methylene chloride solution was dried and then the solvent was distilled off. The residue was purified by column chromatography (eluent: hexane/ethyl acetate 1:1 to ethyl acetate) to obtain liquid. The liquid was precipitated by adding ether to obtain 2.75 g of the desired compound (yield: 39.8%, pale yellow powder).

NMR (200MHz,  $CDCl_3$ )  $\delta$  : 3.11 (2H, t, J=6.5Hz), 3.88 (2H, t, J=6.5Hz), 5.14 (2H, br.s), 6.62 (1H, dd, J=4.9,7.5Hz), 7.71-7.87 (5H, m), 7.98 (1H, dd, J=1.8,4.8Hz).

IR (KBr) $cm^{-1}$ : 3450, 3400, 3300, 1770, 1700.

Example 71

Synthesis of 3-[2-(phthalimido)ethyl]-2-(pivaloylamino)pyridine hydrochloride

In 5 ml of methanol was dissolved 248 mg (0.647 mmol) of 3-[2-(phthalimido)ethyl]-2-(pivaloylamino)pyridine. The solution was treated with 5 ml (10 mmol) of a 2N solution of hydrogen chloride in methanol. The solvent was distilled off to obtain 272 mg of the desired compound (yield: 100%, white powder).

NMR (200MHz,  $D_2O$ )  $\delta$  : 1.27 (9H, s), 3.51 (2H, br.t, J=5.5Hz), 3.92 (2H, br.t, J=5.0Hz), 7.49 (1H, br.t, J=7.0Hz), 7.68-7.77 (4H, m), 8.07 (1H, br.d, J=6.0Hz), 8.53 (1H, br.d, J=8.2Hz).

IR (KBr) $cm^{-1}$ : 3350, 1770, 1710.

Example 72

Synthesis of 2-amino-3-[2-(phthalimido)ethyl]pyridine hydrochloride

In 5 ml of methanol was dissolved 237 mg (0.792 mmol) of 2-amino-3-[2-(phthalimido)ethyl]pyridine. The solution was treated with 5 ml (10 mmol) of a 2N solution of hydrogen chloride in methanol. The solvent was distilled off to obtain the desired powder. The powder thus obtained was washed with ether to obtain 233 mg of the desired compound (yield: 79.0%, pale yellow powder).

NMR (200MHz,  $D_2O$ )  $\delta$  : 3.33 (2H, t, J=5.9Hz), 3.88 (2H, t, J=5.9Hz), 6.70 (1H, dd, J=6.4,7.6Hz), 7.46 (1H, dd, J=1.5,6.3Hz), 7.71-7.78 (4H, m), 8.05 (1H, dd, J=1.5,7.5Hz).

IR (KBr) $cm^{-1}$ : 3280, 3210, 1765, 1710.

Example 73

## Synthesis of 4-[3-(N-benzyl-N-trifluoroacetyl-amino) propylthio]pyridine hydrochloride

## 5 i) Synthesis of 4-(3-hydroxypropylthio)pyridine

In 250 ml of methylene chloride was dissolved 22.2 g (200 mmol) of 4-mercaptopyridine and 27.9 ml (200 mmol) of triethylamine. Thereto was added 18.1 g (200 mmol) of 3-bromo-1-propanol. The mixture was stirred at room temperature for 3 hours. The reaction mixture was washed with a 1N aqueous solution of sodium hydroxide and water and dried. Then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 21.3 g of the desired compound (yield: 62.9%, yellow oil).

NMR (200MHz, CDCl<sub>3</sub>)  $\delta$  : 1.97 (2H, quint., J=7Hz), 3.12 (2H, t, J=7Hz), 3.81 (2H, t, J=7Hz), 7.14 (2H, dd, J=5,2Hz), 8.37 (2H, dd, J=5,2Hz).

IR (neat)cm<sup>-1</sup>: 3350, 2940, 1580.

15

## ii) Synthesis of 4-[3-(N-benzylamino)propylthio]pyridine

In 150 ml of methylene chloride were dissolved 5.22 g (30.8 mmol) of 4-(3-hydroxypropylthio)pyridine and 5.16 ml (37.0 mmol) of triethylamine, methanesulfonyl chloride [2.86 ml (37.0 mmol)] was added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried. Then the solvent was distilled off. 2.62 ml (24.0 mmol) of benzylamine was added to the residue, and the mixture was heated at 80°C for 3 hours. After cooling, the mixture was purified by column chromatography (eluent: chloroform/methanol=25:1) to obtain 1.0 g of the desired compound (yield: 16.1%, yellow oil).

NMR (200MHz, CDCl<sub>3</sub>)  $\delta$  : 1.57 (1H, br.s), 1.90 (2H, quint., J=7.0Hz), 2.79 (2H, t, J=6.8Hz), 3.07 (2H, t, J=7.2Hz), 3.84 (2H, d, J=15.2Hz), 7.11 (2H, dd, J=1.6,4.8Hz), 7.29-7.33 (5H, m), 8.37 (2H, dd, J=1.6,4.8Hz).

## iii) Synthesis of 4-[3-(N-benzyl-N-trifluoroacetyl-amino)propylthio]pyridine

To a solution of 7.27 g (28.1 mmol) 4-[3-(N-benzylamino)propylthio]pyridine and 4.70 ml (33.7 mmol) of triethylamine in 150 ml of methylene chloride, 4.76 ml (33.7 mmol) of trifluoroacetic anhydride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane=2:1 to 1:1) to obtain 6.04 g of 4-[3-(N-benzyl-N-trifluoroacetyl-amino)-propylthio]pyridine (yield: 60.7%, yellow oil).

NMR (200MHz, CDCl<sub>3</sub>)  $\delta$  : 1.80-2.11 (2H, m), 2.91 and 2.93 (2H, t, J=7.4,7.0Hz)†, 3.46 and 3.50 (2H, t, J=7.4,7.0Hz), 4.62 and 4.64 (2H, s)†, 7.02-7.08 (2H, m), 7.19-7.38 (5H, m), 8.41 (2H, m).

†: The peak is split due to the rotational isomers.

## 40 iv) Synthesis of 4-[3-(N-benzyl-N-trifluoroacetyl-amino)propylthio]pyridine hydrochloride

The above free base [1.20 g (3.39 mmol)] was treated with 150 ml of a 10% solution of hydrogen chloride in methanol. The solvent was distilled off to obtain 1.26 g of the desired compound (yield: 95.1%, yellow oil).

NMR (200MHz, D<sub>2</sub>O)  $\delta$  : 1.78-2.21 (2H, m), 3.18-3.28 (2H, m), 3.49-3.73 (2H, m), 4.71 and 4.74 (2H, s)†, 7.27-7.34 (5H, m), 7.63-7.82 (2H, m), 8.35-8.41 (2H, m).

†: The peak is split due to the rotational isomers.

Example 74

## 50 Synthesis of 3-(phthalimidomethylthio)-2-pivaloylaminopyridine

In 3 ml of ethanol were suspended 0.21 g (1.0 mmol) of 3-mercapto-2-(pivaloylamino)pyridine and 0.29 g (1.2 mmol) of (N-bromomethyl)phthalimide, triethylamine [0.14 ml (1.2 mmol)] was added and the mixture was stirred for 4 hours. The solvent was distilled off. The residue was dissolved in chloroform, washed with a saturated aqueous solution of sodium bicarbonate and water and dried. Then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane=2:1) to obtain powder. The powder thus obtained was recrystallized from ethyl acetate to obtain 0.29 g of the desired compound (yield: 78.0%, colorless columns).

Anal. for  $C_{19}H_{19}N_2O_3S$ .

Calcd.: C; 61.77, H; 5.18, N; 11.37

Found: C; 61.78, H; 5.46, N; 11.20.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 1.27 (9H, s); 4.97 (2H, s), 7.08 (1H, dd,  $J=4.8, 7.8$ Hz), 7.70-7.86 (4H, m), 8.01 (1H, dd,  $J=1.8, 7.8$ Hz), 8.41 (1H, dd,  $J=1.8, 7.8$ Hz), 8.55 (1H, bs).

IR (KBr) $cm^{-1}$ : 3200, 2960, 1730, 1720, 1680, 1420, 910, 710.

#### Example 75

##### 10 Synthesis of 4-[3-(N-benzyl-N-acetylamino)propylthio]pyridine

To a solution of 1.0 g (3.87 mmol) of 4-[3-(N-benzylamino)propylthio]-pyridine and 0.65 ml (4.64 mmol) of triethylamine in 25 ml of methylene chloride, 0.49 ml (4.64 mmol) of acetyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: chloroform/methanol=25:1) to obtain 980 mg of the desired compound (yield: 84.2%, yellow oil).

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 1.94 (2H, quint.,  $J=7$ Hz), 2.15 and 2.19 (2H, s) $\ddagger$ , 2.92 and 2.96 (2H, t,  $J=7$ Hz) $\ddagger$ , 3.39 and 3.51 (2H, t,  $J=7$ Hz) $\ddagger$ , 4.53 and 4.61 (2H, s) $\ddagger$ , 7.02-7.13 (2H, m), 7.13-7.42 (5H, m), 8.41 (2H, m).

$\ddagger$ : The peak is split due to the rotational isomers.

IR (neat) $cm^{-1}$ : 3050, 1645, 1580, 800.

#### Example 76

##### 25 Synthesis of 4 [3-(N benzyl-N acetylamino)propylthio]pyridine hydrochloride

The above free base [800 mg (2.66 mmol)] was treated with 50 ml of a 10% solution of hydrogen chloride in methanol. The solvent was distilled off to obtain 794 mg of the desired compound (yield: 90.2%, yellow oil).

NMR (200MHz,  $D_2O$ )  $\delta$ : 1.85-2.03 (2H, m), 2.19 and 2.24 (2H, s) $\ddagger$ , 3.12-3.19 (2H, m), 3.47-3.61 (2H, m), 4.60 and 4.67 (2H, s) $\ddagger$ , 7.25-7.38 (5H, m), 7.69 (2H, bd,  $J=6.0$ Hz), 8.37 (2H, br.d,  $J=6.0$ Hz).

$\ddagger$ : The peak is split due to the rotational isomers.

#### Example 77

##### 35 Synthesis of 4-[3-(N-benzyl-N-benzoylamino)propylthio]pyridine hydrochloride

###### i) Synthesis of 4-[3-(N-benzyl-N-benzoylamino)propylthio]pyridine

To a solution of 400 mg (1.21 mmol) of 4-[3-(N-benzylamino)propylthio]pyridine dihydrochloride and 0.55 ml (4.00 mmol) of triethylamine in 5 ml of methylene chloride, 0.17 ml (1.45 mmol) of benzoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 0.22 g of the desired compound (yield: 50.4%, yellow oil).

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.06 (2H, m), 2.72 and 3.01 (2H, m) $\ddagger$ , 3.35 and 3.59 (2H, m) $\ddagger$ , 4.54 and 4.79 (2H, m) $\ddagger$ , 6.92-7.42 (7H, m), 8.38 (2H, bd,  $J=3$ Hz).

$\ddagger$ : The peak is split due to the rotational isomers.

###### ii) Synthesis of 4-[3-(N-benzyl-N-benzoylamino)propylthio]pyridine hydrochloride

The above free base [0.22 g (0.61 mmol)] was treated with 50 ml of a 10% solution of hydrogen chloride in methanol. The solvent was distilled off to obtain 0.29 g of the desired compound (yield: quant., yellow oil).

NMR (200MHz,  $D_2O$ )  $\delta$ : 1.80-2.08 (2H, m), 2.94 and 3.21 (2H,  $J=6.5$ Hz) $\ddagger$ , 3.39-3.47 and 3.56-3.64 (2H, m) $\ddagger$ , 4.52 and 4.77 (2H, s), 7.15-7.71 (12H, m), 8.34-8.39 (2H, m).

$\ddagger$ : The peak is split due to the rotational isomers.

Example 78

## Synthesis of 4-[3-(N-2-pyridylmethyl-N-trifluoroacetyl-amino)propylthio]pyridine dihydrochloride

## 5 i) Synthesis of 4-[3-(N-2-pyridylmethylamino)propylthio]pyridine

To a solution of 5.26 g (31.1 mmol) of 4-(3-hydroxypropylthio)pyridine and 5.20 ml (37.3 mmol) of triethylamine in 150 ml of methylene chloride, 2.90 ml (37.3 mmol) of methanesulfonyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. To 6.33 g of the residue was added 2.64 ml (25.6 mmol) of 2-aminomethylpyridine. The resulting mixture was heated at 80°C for 3 hours. After cooling, the mixture was purified by column chromatography (eluent: chloroform/methanol=25:1) to obtain 1.62 g of the desired compound (yield: 25.4%, yellow oil).

NMR (200MHz, CDCl<sub>3</sub>) δ : 1.94 (2H, quant., J=7.0Hz), 2.13 (1H, br.s), 2.83 (2H, t, J=6.8Hz), 3.09 (2H, t, J=7.4Hz), 3.92 (2H, s), 7.12 (2H, dd, J=1.6,4.8Hz), 7.28 (1H, dd, J=1.0,5.1Hz), 7.30 (1H, d, J=7.6Hz), 7.66 (1H, dt, J=1.8,7.6Hz), 8.38 (2H, dd, J=1.6,4.8Hz), 8.56 (1H, dd, J=1.0,5.0Hz).

## ii) Synthesis of 4-[3-(N-2-pyridylmethyl-N-trifluoroacetyl-amino)propylthio]pyridine dihydrochloride

To a solution of 1.40 g (5.40 mmol) of 4-[3-(N-2-pyridylmethylamino)propylthio]pyridine and 0.91 ml (6.48 mmol) of triethylamine in 10 ml of methylene chloride, 0.51 ml (6.48 mmol) of trifluoroacetic anhydride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/acetone=10:1) to obtain 390 mg of 4-[3-(N-2-pyridylmethyl-N-trifluoroacetyl-amino)propylthio]pyridine (yield: 20.4%, yellow oil).

NMR (200MHz, CDCl<sub>3</sub>): 1.96 and 2.08 (2H, quant., J=7Hz)‡, 2.95 and 2.97 (2H, t, J=8Hz)‡, 3.59 and 3.68 (2H, t, J=8Hz)‡, 4.72 and 4.74 (2H, s)‡, 7.07 (2H, m), 7.17-7.31 (2H, m), 7.60-7.74 (1H, m), 8.40 (2H, br.s), 8.53 (1H, m).

‡: The peak is split due to the rotational isomers.

The above free base [390 mg (1.10 mmol)] was treated with 70 ml of a 10% solution of hydrogen chloride in methanol. The solvent was distilled off to obtain 418 mg of the desired compound (yield: 89.1%, yellow oil).

NMR (200MHz, D<sub>2</sub>O) δ : 2.18-2.34 (2H, m), 3.24-3.44 (4H, m), 4.55 (2H, s), 7.74=8.04 (4H, m), 8.20-8.29 (1H, m), 8.44 (2H, br.d, J=6.0Hz), 8.70-8.79 (1H, m).

Example 79

## Synthesis of 4-[3-(N-2-pyridylmethyl-N-acetyl-amino)propylthio]pyridine

To a solution of 1.62 g (6.24 mmol) of 4-[3-(N-2-pyridylmethylamino)propylthio]pyridine and 1.10 ml (7.80 mmol) of triethylamine in 10 ml of methylene chloride, 0.51 ml (7.80 mmol) of acetyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/methanol=10:1) to obtain 1.61 g of the desired compound (yield: 85.6%, yellow oil).

NMR (200MHz, CDCl<sub>3</sub>) δ : 1.87-2.03 (2H, m), 2.15 and 2.18 (3H, s)‡, 2.97 and 2.98 (2H, t, J=7Hz)‡, 3.53 and 3.57 (2H, t, J=6Hz)‡, 4.62 and 4.70 (2H, s), 7.06-7.09 (2H, m), 7.14-7.34 (2H, m), 7.60-7.73 (1H, m), 8.43-8.43 (2H, m), 8.49-8.59 (1H, m).

‡: The peak is split due to the rotational isomers.

IR (neat)cm<sup>-1</sup>: 3000, 2940, 1650, 1580.

Example 80

## Synthesis of 4-[3-(N-2-pyridylmethyl-N-acetyl-amino)propylthio]pyridine dihydrochloride

The above free base [1.25 g (4.15 mmol)] was treated with 250 ml of a 10% solution of hydrogen chloride in methanol. The solvent was distilled off to obtain 1.49 g of the desired compound (yield: 95.6%, yellow oil).

NMR (200MHz, D<sub>2</sub>O) δ : 2.04-2.27 (2H, m), 2.17 and 2.28 (3H, s)‡, 3.21-3.38 (2H, m), 3.61 and 3.81

(2H, br.t, J=7.6Hz)±, 4.97 and 5.18 (2H, s)±, 7.79-7.86 (2H, m), 7.93-8.02 (2H, m), 8.42-8.47 (2H, m), 8.52-8.72 (2H, m).

±: The peak is split due to the rotational isomers.

#### 5 Example 81

##### Synthesis of 4-[3-(N-2-pyridylmethyl-N-benzoylamino)propylthio]pyridine

To a solution of 1.60 g (6.17 mmol) of 4-[3-(N-2-pyridylmethylamino)propylthio]pyridine and 1.05 ml (7.40 mmol) of triethylamine in 10 ml of methylene chloride, 0.86 ml (7.40 mmol) of benzoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/methanol=10:1) to obtain 1.32 g of the desired compound (yield: 58.9%, yellow oil).

15 NMR (200MHz, CDCl<sub>3</sub>) δ : 2.02 (2H, m), 2.78 and 3.06 (2H, m)±, 3.49 and 3.76 (2H, m)±, 4.64 and 4.87 (2H, m)±, 6.95-7.23 (4H, m), 7.39 (5H, br.s), 7.69 (5H, br.s), 8.38 (2H, d, J=6Hz), 8.56 (1H, d, J=4Hz).

±: The peak is split due to the rotational isomers.

IR (neat)cm<sup>-1</sup>: 3055, 2940, 1640, 1580.

#### 20 Example 82

##### Synthesis of 4-[3-(N-2-pyridylmethyl-N-benzoylamino)propylthio]pyridine dihydrochloride

The above free base [1.00 g (2.75 mmol)] was treated with 300 ml of a 10% solution of hydrogen chloride in methanol. The solvent was distilled off to obtain 1.15 g of the desired compound (yield: 95.6%, yellow oil).

25 NMR (200MHz, D<sub>2</sub>O) δ : 2.00-2.15 (2H, m), 3.11 (2H, br.t, J=6.0Hz), 3.72-3.84 (2H, m), 5.12 (2H, s), 7.35 7.64 (7H, m), 7.94 8.33 (2H, m), 8.40 (2H, br.d, J=6.2Hz), 8.58 8.79 (2H, m).

#### Example 83

30

##### Synthesis of 4-(3-phthalimidopropoxy)pyridine

To a solution of 4.76 g (50 mmol) of 4-hydroxypyridine and 14.75 g (55 mmol) of N-(3-bromopropyl)phthalimide in 80 ml of DMF was added 8.23 ml (55 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene. The mixture was stirred at room temperature for 6 hours. After the solvent was distilled off, the mixture was poured into water and extracted with ethyl acetate. The mixture was washed with water and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 2.32 g of the desired compound (yield: 16.4%, colorless crystals).

mp: 81.0-82.0°C

40 Anal. for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>.

Calcd.: C; 68.08, H; 5.00, N; 9.92

Found: C; 68.23, H; 5.06, N; 10.00.

NMR (200MHz, CDCl<sub>3</sub>) δ : 2.22 (2H, m), 3.92 (2H, t, J=6.8Hz), 4.08 (2H, t, J=6.2Hz), 6.70 (2H, dd, J=5.1, 4Hz), 7.67-7.92 (4H, m), 8.39 (2H, dd, J=5.1, 4Hz).

45 IR (KBr)cm<sup>-1</sup>: 1775, 1710, 1595, 1565, 1505.

#### Example 84

##### Synthesis of 4-(4-phthalimidobutyloxy)pyridine

50

To a solution of 4.76 g (50 mmol) of 4-hydroxypyridine and 15.52 g (55 mmol) of N-(4-bromobutyl)phthalimide in 80 ml of DMF was added 8.23 ml (5 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene. The mixture was stirred at room temperature for 7 hours. After the solvent was distilled off, the mixture was poured into water and extracted with ethyl acetate. The mixture was washed with water and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 2.63 g of the desired compound (yield: 17.2%, colorless crystals).

mp: 126-127°C

Anal. for C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>·0.5H<sub>2</sub>O.



Calcd.: C: 66.87, H: 5.61, N: 9.17

Found: C: 67.05, H: 5.43, N: 9.20.

NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.75-1.97 (4H, m), 3.78 (2H, m), 4.05 (2H, m), 6.78 (2H, dd,  $J=4.8, 1.6\text{Hz}$ ), 7.88-7.91 (4H, m), 8.41 (2H, dd,  $J=4.8, 1.6\text{Hz}$ ).

IR (KBr) $\text{cm}^{-1}$ : 1770, 1710, 1595, 1570.

#### Example 85

##### Synthesis of 4-[3-(thianaphthene-2-carbonylamino)propyloxy]pyridine

##### i) Synthesis of 4-(3-aminopropoxy)pyridine

Hydrazine monohydrate [2.99 ml (61.6 mmol)] was added to a suspension of 5.80 g (20.5 mmol) of 4-(3-phthalimidopropoxy)pyridine in 50 ml of ethanol, and the mixture was stirred at room temperature for 3 hours. 100 ml of ethyl acetate was added and insoluble materials were filtered off. The volatile component in the filtrate was distilled off and then chloroform was added to the residue. The mixture was washed with brine and dried over potassium carbonate. The solvent was distilled off to obtain 2.99 g of the desired compound (yield: 99.5%, pale yellow oil).

NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.42 (2H, br.), 1.94 (2H, m), 2.91 (2H, t,  $J=6.6\text{Hz}$ ), 4.11 (2H, t,  $J=6.2\text{Hz}$ ), 6.80 (2H, dd,  $J=4.8, 1.6\text{Hz}$ ), 8.41 (2H, dd,  $J=4.8, 1.6\text{Hz}$ ).

##### ii) Synthesis of 4-[3-(thianaphthene-2-carbonylamino)propylthio]pyridine

To a solution of 1.15 g (7.56 mmol) of 4-(3-aminopropoxy)pyridine and 1.27 ml (9.11 mmol) of triethylamine in 50 ml of methylene chloride, 1.49 ml (7.58 mmol) of thianaphthene 2-carbonyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was washed successively with a saturated aqueous solution of sodium bicarbonate and brine and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 1.65 g of the desired compound (yield: 69.1%, pale yellow crystals).

mp: 127-128.5°C.

Anal. for  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2\text{S} \cdot 0.2\text{H}_2\text{O}$ .

Calcd.: C: 64.62, H: 5.23, N: 8.87

Found: C: 64.54, H: 5.20, N: 8.93.

NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.18 (2H, m), 3.70 (2H, m), 4.15 (2H, t,  $J=5.8\text{Hz}$ ), 6.66 (1H, br.), 6.81 (2H, dd,  $J=4.8, 1.6\text{Hz}$ ), 7.34-7.48 (2H, m), 7.75-7.91 (3H, m), 8.43 (2H, dd,  $J=4.8, 1.6\text{Hz}$ ).

IR (KBr) $\text{cm}^{-1}$ : 3370, 1635, 1590, 1570, 1535, 1505, 1280, 1210, 1195.

#### Example 86

##### Synthesis of 4-(3-pivaloylaminopropoxy) pyridine

To a solution of 700 mg (4.60 mmol) of 4-(3-aminopropoxy)pyridine and 0.77 ml (5.52 mmol) of triethylamine in 30 ml of methylene chloride, 0.57 ml (4.63 mmol) of pivaloyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was washed successively with a saturated aqueous solution of sodium bicarbonate and brine and dried over anhydrous magnesium sulfate, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 840 mg of the desired compound (yield: 77.3%, colorless crystals).

mp: 71.5-72.5°C.

Anal. for  $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_2$ .

Calcd.: C: 66.07, H: 8.53, N: 11.85

Found: C: 65.91, H: 8.88, N: 11.71.

NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.20 (9H, s), 2.04 (2H, m), 3.46 (2H, m), 4.09 (2H, t,  $J=6\text{Hz}$ ), 5.98 (1H, br.), 6.80 (2H, dd,  $J=4.8, 1.6\text{Hz}$ ), 8.44 (2H, dd,  $J=4.8, 1.6\text{Hz}$ ).

IR (KBr) $\text{cm}^{-1}$ : 3345, 2970, 1640, 1595, 1570, 1530, 1505, 1285.

Example 87

## Synthesis of 4-(3-nicotinoylaminopropoxy)pyridine

5 To a solution of 700 mg (4.60 mmol) of 4-(3-aminopropoxy)pyridine and 1.54 ml (11.0 mmol) of triethylamine in 30 ml of methylene chloride, 830 mg (4.66 mmol) of nicotinoyl chloride hydrochloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was washed successively with a saturated aqueous solution of sodium bicarbonate and brine and dried over anhydrous magnesium sulfate, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethanol/ethyl acetate=1:10 to 1:5) to obtain 1.05 g of the desired compound (yield: 85.8%, colorless crystals).

mp: 117-119°C.

Anal. for  $C_{14}H_{15}N_3O_2 \cdot 0.2H_2O$ .

Calcd.: C; 64.45, H; 5.95, N; 16.11

15 Found: C; 64.55, H; 5.84, N; 16.03.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.17 (2H, m), 3.71 (2H, m), 4.13 (2H, t, J=5.8Hz), 6.77 (2H, dd, J=4.8, 1.6Hz), 7.03 (1H, br.), 7.39 (1H, m), 8.15 (1H, dt, J=7.8, 2.2Hz), 8.40 (2H, m), 8.73 (1H, dd, J=4.8, 1.6Hz), 9.01 (1H, d, J=2.2Hz).

IR (KBr) $cm^{-1}$ : 3315, 1640, 1590, 1555, 1505, 1475, 1420, 1285, 1215.

Example 88

## Synthesis of 4-(3-caprylaminopropoxy)pyridine

25 To a solution of 700 mg (4.60 mmol) of 4-(3-aminopropoxy)pyridine and 0.77 ml (5.52 mmol) of triethylamine in 30 ml of methylene chloride, 0.96 ml (4.63 mmol) of capryl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was washed successively with a saturated aqueous solution of sodium bicarbonate and brine and dried over anhydrous magnesium sulfate, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 1.05 g of the desired compound (yield: 74.5%, colorless crystals).

mp: 44-46°C.

Anal. for  $C_{18}H_{30}N_2O_2$ .

Calcd.: C; 70.55, H; 9.87, N; 9.14

Found: C; 70.55, H; 9.78, N; 8.82.

35 NMR (200MHz,  $CDCl_3$ )  $\delta$ : 0.88 (3H, m), 1.26 (12H, m), 1.62 (2H, m), 2.03 (2H, m), 2.18 (2H, m), 3.46 (2H, m), 4.07 (2H, t, J=6.0Hz), 5.79 (1H, br.), 6.79 (2H, dd, J=4.8, 1.6Hz), 8.43 (2H, dd, J=4.8, 1.6Hz).

IR (KBr) $cm^{-1}$ : 3290, 2925, 2850, 1640, 1595, 1565, 1555, 1505, 1290, 1210.

Example 89

## Synthesis of 4-[3-(2-thenoylamino)propoxy]pyridine

40 To a solution of 700 mg (4.60 mmol) of 4-(3-aminopropoxy)pyridine and 0.77 ml (5.52 mmol) of triethylamine in 30 ml of methylene chloride, 0.50 ml (4.68 mmol) of thenoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was washed successively with a saturated aqueous solution of sodium bicarbonate and brine and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 850 mg of the desired compound (yield: 70.0%, colorless crystals).

mp: 123-125°C.

Anal. for  $C_{13}H_{14}N_2O_2S \cdot 0.1H_2O$ .

Calcd.: C; 59.12, H; 5.42, N; 10.61

Found: C; 59.01, H; 5.45, N; 10.59.

55 NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.14 (2H, m), 3.65 (2H, m), 4.13 (2H, t, J=6Hz), 6.64 (1H, br.), 6.79 (2H, dd, J=4.8, 1.6Hz), 7.08 (1H, dd, J=4.8, 3.6Hz), 7.48 (2H, dd, J=4.8, 1Hz), 7.54 (1H, dd, J=3.6, 1Hz), 8.42 (2H, dd, J=4.8, 1.6Hz).

IR (KBr) $cm^{-1}$ : 3205, 1635, 1595, 1560, 1505, 1425, 1290, 1210.

Example 90

## Synthesis of 4-[3-(N-(2-thienylmethyl)-N-acetylamino)propylthio]pyridine

5 To a solution of 2.5 g (9.45 mmol) of 4-[3-(N-(2-thienylmethyl)amino)propylthio]pyridine and 1.32 ml (9.45 mmol) of triethylamine in 50 ml of methylene chloride, 0.67 ml (9.45 mmol) of acetyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 1.10 g of the

10 desired compound (yield: 37.9%, yellow oil).  
NMR (200MHz, CDCl<sub>3</sub>)  $\delta$ : 1.84-2.04 (2H, m), 2.14 and 2.22 (3H, s) $\ddagger$ , 2.95 and 2.96 (2H, t, J=6.6, 7.2Hz) $\ddagger$ , 3.45 and 3.54 (2H, t, J=7.6, 7.0Hz) $\ddagger$ , 4.64 and 4.71 (2H, s) $\ddagger$ , 6.89-6.99 (2H, m), 7.08 (2H, dd, J=1.6, 4.6Hz), 7.20-7.27 (1H, m), 8.37-8.43 (2H, m).

$\ddagger$ : The peak is split due to the rotational isomers.

15 IR (neat)cm<sup>-1</sup>: 3040, 1640, 1580, 800, 710.

Example 91

## Synthesis of 4-[3-(N-(2-thienylmethyl)-N-acetylamino)-propylthio]pyridine hydrochloride

20 The above free base [1.01 g (3.3 mmol)] was treated with 80 ml of a 10% solution of hydrogen chloride in methanol. The solvent was distilled off to obtain 1.13 g of the desired compound (yield: quant., yellow oil).

NMR (200MHz, D<sub>2</sub>O)  $\delta$ : 1.86-2.08 (2H, m), 2.18 and 2.24 (3H, s) $\ddagger$ , 3.12-3.23 (2H, m), 3.48-3.65 (2H, m), 4.79 and 4.71 (2H, s) $\ddagger$ , 6.89-7.14 (2H, m), 7.30-7.39 (1H, m), 7.72 (2H, d, J=7.2Hz), 8.40 (2H, d, J=7.0Hz).

25  $\ddagger$ : The peak is split due to the rotational isomers.

Example 92

## Synthesis of 4-[3-(N-(2-thienylmethyl)-N-benzoylamino)propylthio]pyridine

30 To a solution of 2.5 g (9.45 mmol) of 4-[3-(N-(2-thienylmethyl)amino)propylthio]pyridine and 1.32 ml (9.45 mmol) of triethylamine in 50 ml of methylene chloride, 1.1 ml (9.45 mmol) of benzoyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 1.25 g of the

35 desired compound (yield: 35.9%, yellow oil).  
NMR (200MHz, CDCl<sub>3</sub>)  $\delta$ : 1.83-2.31 (2H, br.m), 2.82-3.22 (2H, br.m), 3.35-3.68 (2H, br.m), 4.64-4.85 (2H, br.s), 6.90-7.09 (3H, m), 7.27 (2H, m), 7.42 (5H, s), 8.40 (2H, m).

40 IR (neat)cm<sup>-1</sup>: 3060, 1630, 1580, 800, 700.

Example 93

## Synthesis of 4-[3-(N-(2-thienylmethyl)benzoylamino)propylthio]pyridine hydrochloride

45 The above free base [0.99 g (2.69 mmol)] was treated with 80 ml of a 10% solution of hydrogen chloride in methanol. The solvent was distilled off to obtain 1.09 g of the desired compound (yield: quant., yellow oil).

NMR (200MHz, D<sub>2</sub>O)  $\delta$ : 1.86-2.09 (2H, m), 3.18-3.69 (4H, m), 4.92 (2H, s), 6.92-7.17 (2H, m), 7.29-7.82 (6H, m), 8.38-8.43 (2H, m).

Example 94

## Synthesis of 4-[3-(N-(dodecyl)-N-trifluoroacetyl-amino)propylthio]pyridine

## i) Synthesis of 4-[3-(N-(dodecylamino)propylthio]pyridine

55 In 120 ml of methylene chloride was dissolved 5.60 g (33.1 mmol) of 4-(3-hydroxypropylthio)pyridine and 5.53 ml (39.7 mmol) of triethylamine. 3.07 ml (39.7 mmol) of methanesulfonyl chloride was added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous

solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. 5.34 g (28.8 mmol) of dodecylamine was added to 7.12 g of the residue, and the mixture was heated at 80°C for 3 hours. After cooling, the mixture was purified by column chromatography (eluent: chloroform/methanol=25:1) to obtain 2.86 g of the desired compound (yield: 29.5%, yellow oil).

NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  : 0.88 (3H, br.t,  $J=6.8\text{Hz}$ ), 1.22-1.40 (18H, m), 1.42-1.58 (2H, m), 1.93 (2H, quint.,  $J=7.4\text{Hz}$ ), 2.21 (1H, br.s), 2.63 (2H, t,  $J=7.4\text{Hz}$ ), 2.80 (2H, t,  $J=6.8\text{Hz}$ ), 3.06 (2H, t,  $J=7.4\text{Hz}$ ), 7.12 (2H, dd,  $J=1.6, 4.6\text{Hz}$ ), 8.38 (2H, dd,  $J=1.6, 4.6\text{Hz}$ ).

IR (neat) $\text{cm}^{-1}$ : 3300, 3035, 2930, 2860, 1580, 805, 715.

#### ii) Synthesis of 4-[3-(N-dodecyl-N-trifluoroacetylthio)propylthio]pyridine

To a solution of 2.86 g (8.5 mmol) of 4-[3-(N-dodecylamino)propylthio]pyridine and 1.2 ml (8.5 mmol) of triethylamine in 30 ml of methylene chloride, 1.2 ml (8.5 mmol) of trifluoroacetic anhydride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and water and dried, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane=1:1) to obtain 1.72 g of the desired compound (yield: 48.6%, yellow oil).

NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  : 0.88 (3H, t,  $J=7.6\text{Hz}$ ), 1.21-1.33 (16H, m), 1.53-1.65 (2H, m), 2.02 (2H, quint.,  $J=7.8\text{Hz}$ ), 3.00 (2H, dt,  $J=1.8, 7.0\text{Hz}$ ), 3.35 (2H, bt,  $J=7.6\text{Hz}$ ), 3.53 (2H, bt,  $J=7.6\text{Hz}$ ), 7.14 (2H, dd,  $J=1.6, 4.6\text{Hz}$ ), 8.41 (2H, dd,  $J=1.6, 4.6\text{Hz}$ ).

IR (neat) $\text{cm}^{-1}$ : 2930, 1690, 1580, 800, 710.

#### Example 95

#### 25 Synthesis of 4-[(4-nitrophthalimido)methylthio]pyridine

N-chloromethyl-4-nitrophthalimide [2.89 g (12 mmol)] was added under ice-cooling with stirring to a suspension of 1.11 g (10 mmol) of 4-mercaptopyridine and 1.4 ml (12 mmol) of triethylamine in 50 ml of ethanol. The mixture was stirred at room temperature for 16 hours. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to obtain 1.99 g of the desired compound (yield: 63.1%, yellow crystals).

NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  : 5.25 (2H, m), 7.40 (2H, dd,  $J=1.8, 4.6\text{Hz}$ ), 8.08 (1H, d,  $J=8.0\text{Hz}$ ), 8.48 (2H, dd,  $J=1.8, 4.6\text{Hz}$ ), 8.63 (1H, dd,  $J=1.8, 8.0\text{Hz}$ ).

IR (KBr) $\text{cm}^{-1}$ : 3100, 1725, 1535, 1345.

#### Example 96

#### Synthesis of 4-[cis-(1,2,3,6-tetrahydrophthalimido)methylthio]pyridine

#### 40 i) Synthesis of cis-(N-hydroxymethyl)-1,2,3,6-tetrahydrophthalimide

Formalin [8.1 ml (100 mmol)] was added to a suspension of 15.12 g (100 mmol) of cis-1,2,3,6-tetrahydrophthalimide in 150 ml of water. The mixture was stirred for about 1 hour under heating at 110°C until the precipitate was dissolved and the mixture became a clear solution. The reaction mixture was filtered while it was hot, and then was allowed to stand overnight in a refrigerator. The resulting precipitate was filtered off, washed with ice water and then dried to obtain 17.48 g of the desired compound (yield: 96.5%, pale yellow solid).

Anal. for  $\text{C}_9\text{H}_{11}\text{NO}_3$ .

Calcd.: C; 59.66, H; 6.12, N; 7.73

Found: C; 59.96, H; 6.27, N; 7.76.

NMR (200MHz,  $\text{DMSO}-d_6$ )  $\delta$  : 5.00 (2H, d,  $J=6.8\text{Hz}$ ), 6.50 (1H, t,  $J=6.8\text{Hz}$ ), 7.95 (1H, dd,  $J=1.0, 4.8\text{Hz}$ ), 9.14 (1H, d,  $J=4.8\text{Hz}$ ), 9.19 (1H, d,  $J=1.0\text{Hz}$ ).

IR (KBr) $\text{cm}^{-1}$ : 3480, 3045, 2950, 1700.

#### ii) Synthesis of cis-(N-bromomethyl)-1,2,3,6-tetrahydrophthalimide

Triphenylphosphine [3.15 g (12 mmol)] was added to a solution of 1.81 g (10 mmol) of cis-(N-hydroxymethyl)-1,2,3,6-tetrahydrophthalimide and 3.98 g (12 mmol) of carbon tetrachloride in 100 ml of methylene chloride. The mixture was stirred at room temperature for 16 hours. The solvent was distilled off and then the residue

was purified by column chromatography (eluent: ethyl acetate/hexane=1:2) to obtain 1.25 g of the desired compound (yield: 51.2%, brown oil).

NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  : 2.27 (2H, m), 2.63 (2H, m), 3.16 (2H, m), 5.17 (2H, s), 5.91 (2H, m).

IR (neat) $\text{cm}^{-1}$ : 3050, 2950, 1730, 1710, 655, 600.

5

### iii) Synthesis of 4-[cis-(1,2,3,6-tetrahydrophthalimido)methylthio]pyridine

To a suspension of 110 mg (1.0 mmol) of 4-mercaptopyridine and 0.14 ml (1.2 mmol) of triethylamine in 5 ml of ethanol, 2.93 mg (1.2 ml) of cis-(N-bromomethyl)-1,2,3,6-tetrahydrophthalimide was added under ice-cooling with stirring. The mixture was stirred at room temperature for 16 hours. The solvent was distilled off and then the residue was purified by column chromatography (eluent: ethyl acetate) to obtain 250 mg of the desired compound (yield: 91.0%, yellow oil).

NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  : 2.17-2.27 (2H, m), 2.53-2.64 (2H, m), 3.11 (2H, m), 4.93 (2H, m), 5.80 (2H, m), 7.34 (2H, dd,  $J=1.2, 4.2\text{Hz}$ ), 8.44 (2H, bd,  $J=4.2\text{Hz}$ ).

IR (neat) $\text{cm}^{-1}$ : 3040, 2950, 1710, 1570.

15

### Example 97

#### Synthesis of 4-(3-hydroxyisoindolin-1-on-2-ylmethylthio)pyridine

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To a solution of 4.01 g (14.8 mmol) of 4-(phthalimidomethylthio)pyridine in 25 ml of methanol, a solution of 1.08 g (29.7 mmol) of sodium borohydride in 20 ml of methanol was added. The mixture was stirred at room temperature for 4 hours. Glacial acetic acid (0.5 ml) was added to quench the reaction, and then the solvent was distilled off. The residue was dissolved in chloroform, washed with water and dried, and the solvent was distilled off. The residue was purified by recrystallization (recrystallization solvent: ethanol) to obtain 2.35 g of the desired compound (yield: 58.3%, yellow crystals).

Anal. for  $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ ,

Calcd.: C; 61.75, H; 4.44, N; 10.29

Found: C; 61.51, H; 4.39, N; 10.40.

30

NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  : 4.77 (1H, d,  $J=14.2\text{Hz}$ ), 4.78 (1H, bs), 5.49 (1H, d,  $J=14.2\text{Hz}$ ), 6.01 (1H, bs), 7.30-7.33 (2H, m), 7.46-7.77 (4H, m), 8.17-8.12 (2H, m).

IR (KBr) $\text{cm}^{-1}$ : 3420, 3140, 3050, 1700.

### Example 98

35

#### Synthesis of 4-(2-phthalimidoethoxy)pyridine

To a solution of 4.76 g (50 mmol) of 4-hydroxypyridine and 13.97 g (55 mmol) of N-(2-bromoethyl)phthalimide in 80 ml of DMF, 8.23 ml (55 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added. The mixture was stirred at room temperature for 32 hours. After the solvent was distilled off, the mixture was poured into water and extracted with ethyl acetate. The mixture was washed with water and dried over anhydrous magnesium sulfate, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to obtain 0.41 g of the desired compound (yield: 3.1%, colorless crystal).

mp: 157-158°C

45

NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  : 4.14 (2H, m), 4.29 (2H, m), 6.80 (2H, dd,  $J=4.8, 1.6\text{Hz}$ ), 7.69-7.93 (4H, m), 8.41 (2H, dd,  $J=4.8, 1.6\text{Hz}$ ).

IR (KBr)  $\text{cm}^{-1}$ : 1775, 1705, 1595, 1570, 1510, 1290.

### Example 99

50

#### Synthesis of 4-[3-(3-hydroxyisoindolin-1-on-2-yl)propyloxy]pyridine

Sodium borohydride [1.89 g (50 mmol)] was added to a solution of 2.82 g (10.0 mmol) of 4-(3-phthalimidopropoxy)pyridine in 150 ml of ethanol. The mixture was stirred at room temperature for 15 minutes. After the solvent was distilled off, brine was added to the residue. The mixture was extracted with chloroform and dried over anhydrous magnesium sulfate, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethanol/ethyl acetate=1:10), and then recrystallized from ethyl acetate to obtain 1.54 g of the desired compound (yield: 54.2%, colorless crystals).

mp: 124-125°C.

Anal. for  $C_{16}H_{16}N_2O_3$ .

Calcd.: C; 67.59, H; 5.67, N; 9.85

Found: C; 67.74, H; 5.74, N; 9.84.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.04-2.36 (2H, m), 3.60-4.05 (4H, m), 5.22 (1H, br.), 5.85 (1H, s), 6.55 (1H, dd,  $J=4.8, 1.6$ Hz), 7.47-7.67 (3H, m), 7.79 (1H, m), 7.97 (2H, dd,  $J=4.8, 1.6$ Hz).

IR (KBr) $cm^{-1}$ : 3115, 1685, 1605, 1570, 1505, 1470, 1445, 1420, 1290, 1215.

#### Example 100

##### Synthesis of 4-[3-(2-hydroxymethylbenzoyl)aminopropoxy]pyridine

Sodium borohydride [3.78 g (100 mmol)] was added to a solution of 2.82 g (10.0 mmol) of 4-(3-phthalimidopropoxy)pyridine in 150 ml of ethanol. The mixture was stirred at room temperature for 3 hours. After the solvent was distilled off, brine was added to the residue. The mixture was extracted with chloroform and dried over anhydrous magnesium sulfate. The solvent was distilled off and then the residue was purified by column chromatography (eluent: ethanol/ethyl acetate=1:10) to obtain 1.488 g of the desired compound (yield: 52.0%, colorless crystals).

mp: 108-109°C.

Anal. for  $C_{13}H_{18}N_2O_3$ .

Calcd.: C; 67.12, H; 6.34, N; 9.78

Found: C; 67.20, H; 6.40, N; 9.68.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.16 (2H, m), 3.67 (2H, m), 4.13 (2H, t,  $J=6$ Hz), 4.61 (2H, s), 4.75 (1H, br.), 6.76 (2H, dd,  $J=4.8, 1.6$ Hz), 7.28 (1H, br.), 7.30-7.50 (3H, m), 7.59 (1H, m), 8.33 (2H, dd,  $J=4.8, 1.6$ Hz).

IR (KBr)  $cm^{-1}$ : 3400, 3205, 1635, 1600, 1585, 1565, 1510, 1440.

#### Example 101

##### Synthesis of 4-[3-(isoindolin-1-on-2-yl)propoxy]pyridine

To a solution of 1.25 ml (9.0 mmol) of 4-[3-(2-hydroxymethylbenzoyl)-aminopropoxy]pyridine and 1.25 ml (9.0 mmol) of triethylamine in 50 ml of methylene chloride, 0.47 ml (6.1 mmol) of methanesulfonyl chloride was added under ice-cooling with stirring. The mixture was stirred at room temperature for 15 minutes. The reaction mixture was washed successively with a saturated aqueous solution of sodium bicarbonate, water and brine and dried over anhydrous magnesium sulfate, and then the solvent was distilled off. The residue was purified by column chromatography (eluent: ethanol/ethyl acetate=1:10) to obtain 537 mg of the desired compound (yield: 66.6%, pale brown crystals).

mp: 70-71°C.

Anal. for  $C_{16}H_{16}N_2O_2$ .

Calcd.: C; 71.62, H; 6.01, N; 10.44

Found: C; 71.47, H; 6.07, N; 10.33.

NMR (200MHz,  $CDCl_3$ )  $\delta$ : 2.17 (2H, m), 3.69 (2H, t,  $J=6.6$ Hz), 4.18 (2H, t,  $J=6.4$ Hz), 5.29 (2H, s), 6.82 (2H, dd,  $J=4.8, 1.6$ Hz), 7.33-7.56 (3H, m), 7.83 (1H, m), 8.40 (2H, dd,  $J=4.8, 1.6$ Hz).

IR (KBr) $cm^{-1}$ : 1685, 1590, 1565, 1505, 1465, 1290, 1215.

#### Example 102

##### Synthesis of 4-(3,4-pyridinedicarboxyimidomethylthio)pyridine

##### i) Synthesis of (N-hydroxymethyl)-3,4-pyridinedicarboxyimide

Formalin [0.81 ml (10.0 mmol)] was added to a suspension of 1.48 g (10.0 mmol) of 3,4-pyridinecarboxyimide in 17.5 ml of water. The mixture was stirred for about 1 hour under heating at 110°C until the precipitate was dissolved and the mixture became a clear solution. The reaction mixture was filtered while it was hot, and then was allowed to stand overnight in a refrigerator. The resulting precipitate was filtered off, washed with ice water and then dried to obtain 0.34 g of the desired compound (yield: 19.0%, pale red yellow solid).

Anal. for  $C_8H_6N_2O_3 \cdot 0.1H_2O$ .

Calcd.: C; 3.40, H; 3.47, N; 15.57

Found : C; 53.28, H; 3.37, N; 15.57.

NMR (200MHz, DMSO- $d_6$ )  $\delta$  : 5.00 (2H, d, J=6.8Hz), 6.50 (1H, t, J=6.8Hz), 7.95 (1H, dd, J=1.0,4.8Hz), 9.14 (1H, d, J=4.8Hz), 9.19 (1H, d, J=1.0Hz).

IR (KBr) $\text{cm}^{-1}$ : 3170, 1785, 1710.

## ii) Synthesis of 4-(3,4-pyridinedicarboxyimidomethylthio)pyridine

Thionyl chloride [0.22 ml (3.0 mmol)] was added to a suspension of 180 mg (1.0 mmol) of (N-hydroxymethyl)-3,4-pyridinedicarboxyimide in 5 ml of carbon tetrachloride. The mixture was stirred under heating at 80°C for 3 hours. After cooling, the solvent was distilled off. 0.42 ml (3.0 mmol) of triethylamine and 110 mg (1.0 mmol) of 4-mercaptopyridine were added to a suspension of the residue in 5 ml of ethanol. The mixture was stirred at room temperature for 16 hours. The solvent was distilled off. Then the residue was dissolved in chloroform, washed with water and dried. The solvent was distilled off and then the residue was purified by column chromatography (eluent: ethyl acetate) to obtain 70 mg of the desired compound (yield: 27%, yellow crystals).

NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  : 5.22 (2H, s), 7.40 (2H, dd, J=1.6,4.6Hz), 7.78 (1H, dd, J=1.0,4.8Hz), 8.47 (2H, dd, J=1.6,4.6Hz), 9.11 (1H, d, J=4.8Hz), 9.20 (1H, d, J=1.0Hz).

IR (KBr) $\text{cm}^{-1}$ : 1720, 1580, 920, 810, 740.

## Example 103

### Synthesis of 4-[2-(2-hydroxymethylbenzoyl)amino ethylthio]pyridine

To a solution of 2.84 g (10.0 mmol) of 4-(2-phthalimidoethylthio)pyridine in 150 ml of ethanol, 3.78 g (100 mmol) of sodium borohydride was added, and the mixture was stirred at room temperature for 3 hours. The solvent was distilled off and saturated saline was added to the residue. The mixture was extracted with chloroform and the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethanol/ethyl acetate = 1 : 10) to give 2.24 g of the desired compound (77.8% yield, colorless crystals), mp. 132-133°C.

Anal. for  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ ,

Calcd.: C; 62.48, H; 5.59, N; 9.71.

Found: C; 62.20, H; 5.65, N; 9.53.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  : 3.30 (2H, t, J=6.6 Hz), 3.76 (2H, m), 4.20 (1H, br), 4.64 (2H, ABq), 6.99 (1H, br), 7.23 (2H, dd, J=4.8, 1.6 Hz), 7.31-7.58 (4H, m), 8.42 (2H, dd, J=4.8, 1.6 Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3260, 1655, 1590, 1555.

## Example 104

### Synthesis of 4-[2-(3-hydroxyisoindolin-1-on-2-yl)ethylthio]pyridine

To a solution of 5.69 g (20.0 mmol) of 4-(2-phthalimidoethylthio)pyridine in 150 ml of ethanol, 2.27 g (60 mmol) of sodium borohydride was added, and the mixture was stirred at room temperature for 15 minutes. The solvent was distilled off and saturated saline was added to the residue. The mixture was extracted with chloroform and the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethanol/ethyl acetate = 1 : 10), after which subsequent recrystallization from ethyl acetate gave 3.63 g of the desired compound (63.4% yield, colorless crystals), mp. 111.5-112.5°C.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  : 3.31 (2H, t, J=7.2 Hz), 3.79 (2H, m), 5.89 (1H, s), 7.23 (2H, dd, J=6.4, 1.6 Hz), 7.42-7.65 (3H, m), 7.50 (1H, dd, J=6.8, 1.2 Hz), 8.21 (2H, m).

IR (KBr)  $\text{cm}^{-1}$ : 3510, 3435, 1700, 1680, 1585.

## Example 105

### Synthesis of 4-[2-(isoindolin-1-on-2-yl)ethylthio]pyridine

To a solution of 1.153g (4.0 mmol) of 4-[2-(2-hydroxymethylbenzoyl)aminoethylthio]pyridine and 1.68 ml (12.1 mmol) of triethylamine in 50 ml of methylene chloride, 0.62 ml (8.0 mmol) of methanesulfonyl chloride was added with stirring at room temperature, and the mixture was stirred at room temperature for 30 minutes. The mixture was washed with saturated aqueous sodium bicarbonate, water and saturated saline, and dried

over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 623 mg of the desired compound (57.6% yield, colorless crystals), mp. 86-87°C.

Anal. for  $C_{15}H_{14}N_2OS$ .

5 Calcd.: C; 66.64, H; 5.22, N; 10.36.

Found: C; 66.49, H; 5.25, N; 10.26.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 3.29 (2H, m), 3.84 (2H, m), 5.34 (2H, s), 7.22 (2H, dd,  $J=4.6, 1.6$  Hz), 7.34-7.58 (3H, m), 7.83 (1H, d,  $J=7.6$  Hz), 8.38 (2H, dd,  $J=4.6, 1.6$  Hz).

IR (KBr)  $cm^{-1}$ : 1705, 1695, 1575.

10

#### Example 106

##### Synthesis of 4-[4-(2-hydroxymethylbenzoyl)aminobutylthio]pyridine

15 To a solution of 6.25 g (20.0 mmol) of 4-(4-phthalimidobutylthio)pyridine in 300 ml of ethanol, 7.57 g (200 mmol) of sodium borohydride was added, and the mixture was stirred at room temperature for 14 hours. The solvent was distilled off and saturated saline was added to the residue. The mixture was extracted with chloroform and the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethanol/ethyl acetate = 1 : 10) to give 4.63 g of the desired  
20 compound (73.1% yield, colorless crystals), mp. 87-88°C.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.83 (4H, m), 3.06 (2H, m), 3.52 (2H, m), 4.60 (2H, s), 6.63 (1H, br), 7.13 (2H, dd,  $J=6.4, 1.6$  Hz), 7.25-7.58 (4H, m), 8.37 (2H, m).

IR (KBr)  $cm^{-1}$ : 3300, 1655, 1590, 1560.

#### 25 Example 107

##### Synthesis of 4-[4-(3-hydroxyisoindolin-1-on-2-yl)butylthio]pyridine

To a solution of 6.25 g (20.0 mmol) of 4-(4-phthalimidobutylthio)pyridine in 300 ml of ethanol, 1.51 g (40  
30 mmol) of sodium borohydride was added, and the mixture was stirred at room temperature for 2.5 hours. The solvent was distilled off and saturated saline was added to the residue. The mixture was extracted with chloroform and the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 1.73 g of the desired compound (27.5%  
35 yield, colorless crystals), mp. 144-145°C.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.82 (4H, m), 3.04 (2H, t,  $J=7.2$  Hz), 3.45-3.75 (2H, m), 5.80 (1H, s), 7.13 (2H, dd,  $J=4.8, 1.6$  Hz), 7.45-7.65 (3H, m), 7.74 (1H, m), 8.25 (2H, m).

IR (KBr)  $cm^{-1}$ : 1700, 1585.

#### 40 Example 108

##### Synthesis of 4-[3-(2-hydroxymethylbenzoyl)aminopropylthio]pyridine

To a solution of 5.97 g (20.0 mmol) of 4-(3-phthalimidopropylthio)pyridine in 300 ml of ethanol, 7.57 g (200  
45 mmol) of sodium borohydride was added, and stirred at room temperature for 24 hours. The solvent was distilled off and saturated saline was added to the residue. The mixture was extracted with chloroform and the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethanol/ethyl acetate = 1 : 10) to give 4.73 g of the desired compound (78.2%  
50 yield, colorless crystals), mp. 110-111°C.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.08 (2H, m), 3.11 (2H, t,  $J=7.2$  Hz), 3.64 (2H, m), 4.62 (2H, s), 6.81 (1H, br), 7.16 (2H, dd,  $J=4.8, 1.6$  Hz), 7.32-7.52 (3H, m), 7.57 (1H, d,  $J=7.6$  Hz), 8.38 (2H, dd,  $J=4.8, 1.6$  Hz).

IR (KBr)  $cm^{-1}$ : 3280, 1655, 1585, 1555.

#### Example 109

##### 55 Synthesis of 4-[4-(isoindolin-1-on-2-yl)butylthio]pyridine

To a solution of 1.58 g (5.0 mmol) of 4-[4-(2-hydroxymethylbenzoyl)aminobutylthio]pyridine and 2.09 ml (15.0 mmol) of triethylamine in 50 ml of methylene chloride, 0.77 ml (10.0 mmol) of methanesulfonyl chloride



was added with stirring at room temperature, and the mixture was stirred at room temperature for 30 minutes. The mixture was washed with saturated aqueous sodium bicarbonate, water and saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 1.075 g of the desired compound (72.1% yield, pale brown crystals), mp. 57-58°C.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.87 (4H, m), 3.05 (2H, m), 3.59 (2H, m), 5.36 (2H, s), 7.11 (2H, dd,  $J=4.8$ , 1.6 Hz), 7.34-7.59 (3H, m), 7.97 (1H, d,  $J=7.2$  Hz), 8.35 (2H, dd,  $J=4.8$ , 1.6 Hz).

IR (KBr)  $\text{cm}^{-1}$ : 1685, 1580, 1535, 1485, 1470, 1460, 1415, 1375, 1350.

#### 10 Example 110

##### Synthesis of 4-[3-(3-hydroxyisoindolin-1-on-2-yl)propylthio]pyridine

To a solution of 5.97 g (20.0 mmol) of 4-(3-phthalimidopropylthio)pyridine in 300 ml of ethanol, 1.51 g (40 mmol) of sodium borohydride was added, and the mixture was stirred at room temperature for 5 hours. The solvent was distilled off and saturated saline was added to the residue. The mixture was extracted with chloroform and the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethanol/ethyl acetate = 1 : 10) to give 3.27 g of the desired compound (54.4% yield, colorless crystals), mp. 132-134°C.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.11 (2H, m), 2.97 (2H, m), 3.72 (2H, m), 5.83 (1H, s), 6.98 (2H, d,  $J=5.4$  Hz), 7.47-7.67 (3H, m), 7.77 (1H, dd,  $J=7.6$ , 1.2 Hz), 8.02 (2H, m).

IR (KBr)  $\text{cm}^{-1}$ : 3430, 1690, 1585, 1470, 1415, 1350.

#### 25 Example 111

##### Synthesis of 4-[3-(isoindolin-1-on-2-yl)propylthio]pyridine

To a solution of 1.51 g (5.0 mmol) of 4-[3-(2-hydroxymethylbenzoyl)aminopropylthio]pyridine and 2.09 ml (15.0 mmol) of triethylamine in 50 ml of methylene chloride, 0.77 ml (10.0 mmol) of methanesulfonyl chloride was added with stirring at room temperature, and the mixture was stirred at room temperature for 30 minutes. The mixture was washed with saturated aqueous sodium bicarbonate, water and saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 1.12g of the desired compound (78.9% yield, pale brown crystals), mp. 73-74.5°C.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.11 (2H, m), 3.16 (2H, m), 3.68 (2H, t,  $J=6.6$  Hz), 5.37 (2H, s), 7.17 (2H, dd,  $J=6.6$ , 1.6 Hz), 7.36-7.61 (3H, m), 8.01 (1H, d,  $J=7.6$  Hz), 8.35 (2H, dd,  $J=6.6$ , 1.6 Hz).

IR (KBr)  $\text{cm}^{-1}$ : 1690, 1580.

#### 40 Example 112

##### Synthesis of 4-[(2-methylcarbamoylbenzoyl)aminomethylthio]pyridine

To a solution of 6.76 g (25.0 mmol) of 4-phthalimidomethylthiopyridine in 100 ml of chloroform, 5 ml of 40% methylamine-methanol solution was added, and the mixture was stirred at room temperature for 3 hours. Additional 5 ml of 40% methylamine-methanol solution was added, and the mixture was stirred at room temperature for 3 hours. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethanol/ethyl acetate = 1 : 10), and the resulting crude product was crystallized from methylene chloride-diethylether to give 2.645 g of the desired compound (35.1% yield, yellow crystals), mp. 118-121°C.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.81 (3H, d,  $J=5.0$  Hz), 4.97 (2H, d,  $J=6.2$  Hz), 6.46 (1H, br), 7.32 (2H, dd,  $J=4.8$ , 1.6 Hz), 7.36-7.71 (4H, m), 8.24 (1H, br), 8.39 (2H, dd,  $J=4.8$ , 1.6 Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3550, 3295, 1645, 1620, 1585, 1540.

#### 55 Example 113

##### Synthesis of 4-(3-phthalimidopropoxy)pyridine hydrochloride

To a solution of 1.41 g (5.0 mmol) of 4-(3-phthalimidopropoxy)pyridine in 20 ml of methanol, 10 ml of hydrogen chloride-methanol was added. The solvent was distilled off and acetone was added to the residue. The

resulting crystals were collected by filtration and washed with acetone to give 1.03 g of the desired compound (64.8% yield, colorless crystals), mp. 167-169°C.

NMR (200 MHz, DMSO- $d_6$ )  $\delta$ : 2.15 (2H, m), 3.78 (2H, t, J=6.6 Hz), 4.39 (2H, t, J=6.2 Hz), 7.45 (2H, d, J=7.2 Hz), 7.86 (4H, m), 8.73 (2H, d, J=7.2 Hz).

IR (KBr)  $\text{cm}^{-1}$ : 1780, 1715, 1640, 1595, 1510.

#### Example 114

##### Synthesis of 4-(4-phthalimidobutyloxy)pyridine hydrochloride

To a suspension of 1.48 g (5.0 mmol) of 4-(4-phthalimidobutyloxy)pyridine in 20 ml of methanol, 15 ml of hydrogen chloride-methanol was added and dissolve. The solvent was distilled off and the residue was crystallized from acetone-ether. The resulting crystals were collected by filtration and washed with ether to give 1.51 g of the desired compound (86.3% yield, colorless crystals), mp. 154-156°C.

Anal. for  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3\text{S}\cdot\text{HCl}\cdot\text{H}_2\text{O}$ ,

Calcd.: C; 58.21, H; 5.46, N; 7.99.

Found: C; 58.29, H; 5.38, N; 8.02.

NMR (200 MHz, DMSO- $d_6$ )  $\delta$ : 1.81 (4H, m), 3.66 (2H, m), 4.37 (2H, m), 7.54 (2H, d, J=7.4 Hz), 7.87 (9H, m), 8.74 (2H, d, J=7.4 Hz).

IR (KBr)  $\text{cm}^{-1}$ : 1770, 1715, 1640, 1595, 1510.

#### Example 115

##### Synthesis of 4-[3-(thianaphthene-2-carbonyl)aminopropoxy]pyridine hydrochloride

To a solution of 625 mg (2.0 mmol) of 4-[3-(thianaphthene-2 carbonyl)aminopropoxy]pyridine in 20 ml of methanol, 10 ml of hydrogen chloride-methanol was added. The solvent was distilled off and the residue was crystallized from acetone-ether. The resulting crystals were collected by filtration and washed with ether to give 650 mg of the desired compound (93.1% yield, colorless crystals), mp. 163-165°C.

NMR (200 MHz, DMSO- $d_6$ )  $\delta$ : 2.10 (2H, m), 3.47 (2H, m), 4.43 (2H, t, J=6.2 Hz), 7.37-7.60 (2H, m), 7.87-8.06 (2H, m), 8.11 (1H, s), 8.75 (2H, d, J=7.2 Hz), 8.94 (1H, br).

IR (KBr)  $\text{cm}^{-1}$ : 3430, 1645, 1545, 1510.

#### Example 116

##### Synthesis of 4-phthalimidomethyloxypyridine hydrochloride

To a solution of 1.27 g (5.0 mmol) of 4-phthalimidomethyloxypyridine in 20 ml of methylene chloride, 10 ml of hydrogen chloride-methanol was added. The solvent was distilled off and acetone was added to the residue. The resulting crystals were collected by filtration and washed with acetone to give 1.35 g (93.1% yield, colorless crystals); mp. 157-159°C.

Anal. for  $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_3\cdot\text{HCl}$ ,

Calcd.: C; 57.84, H; 3.81, N; 9.64.

Found: C; 57.74, H; 3.82, N; 9.69.

NMR (200 MHz, DMSO- $d_6$ )  $\delta$ : 5.96 (2H, s), 7.73 (2H, t, J=6 Hz), 7.88-8.06 (4H, m), 8.83 (2H, d, J=6.2 Hz).

IR (KBr)  $\text{cm}^{-1}$ : 1785, 1725, 1640, 1505.

#### Example 117

##### Synthesis of 4-[2-(N-benzyl-N-benzoyl)aminoethoxy]pyridine

To a solution of 2.55 g (10 mmol) of N-benzyl N-benzoyl ethanolamine in 30 ml of DMF, 800 mg (20 mmol) of 60% sodium hydride (oily) was added with stirring under ice-cooling, and the mixture was stirred for 5 minutes. Then, 1.94 g (10 mmol) of 4-bromopyridine hydrochloride was added, and the mixture was stirred at room temperature for 7 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The extract was washed two times with water and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 1.97 g of the desired

compound (59.3% yield, pale yellow oil).

NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.68-4.98 (6H, m), 6.55-7.55 (12H, m), 8.44 (2H, m).

IR (neat) cm<sup>-1</sup>: 1635, 1500, 1460, 1420, 1285.

#### 5     Example 118

##### Synthesis of 4-[2-(N-benzyl-N-benzoyl)aminoethoxy]pyridine hydrochloride

10     To a solution of 0.71 g (2.78 mmol) of 4-[2-(N-benzyl-N-benzoyl)aminoethoxy]pyridine in 20 ml of methanol, 15 ml of hydrogen chloride-methanol was added. The solvent was distilled off and acetone was added to the residue. The solvent was distilled off and toluene was further added to the residue. The solvent was distilled off and the residue was crystallized from acetone. The resulting crystals were collected by filtration and washed with acetone to give 585 mg of the desired compound (74.2% yield, colorless crystals), mp. 150-152°C.

15     NMR (200 MHz, DMSO-d<sub>6</sub>)  $\delta$ : 3.70 (2H, m), 4.30-4.90 (4H, m), 7.17-7.65 (12H, m), 8.74 (2H, m).

IR (KBr) cm<sup>-1</sup>: 1640, 1625, 1605, 1505.

#### Example 119

##### Synthesis of 4-[2-(N-benzyl-N-trifluoroacetyl-amino)ethylthio]pyridine

20

##### i) Synthesis of N-benzyl-N-trifluoroacetyl-aminoethanol

25     To a solution of 14.2 ml (100 mmol) of N-benzylaminoethanol and 14.3 ml (205 mmol) of triethylamine in 200 ml of methylene chloride, 14.5 ml (205 mmol) of anhydrous trifluoroacetic anhydride was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate and water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 1) to give 20.12 g of the desired compound (81.4% yield, yellow oil).

30     NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.70 (1H, bs), 3.51 and 3.54 (2H, t, J=5.2, 5.6 Hz)†, 3.77 and 3.80 (2H, t, J=5.4 Hz)†, 4.76 and 4.81 (2H, s)†, 7.21-7.40 (5H, m). †: The peak is split due to the rotational isomers.

IR (neat) cm<sup>-1</sup>: 3450, 3025, 1680, 1450, 760, 700.

##### ii) Synthesis of 4-[2-(N-benzyl-N-trifluoroacetyl-amino)ethylthio]pyridine

##### 35     a) Process by way of mesylate

40     N-Benzyl-N-trifluoroacetyl-aminoethanol [2.0 g (8.1 mmol)] and 1.35 ml (9.7 mmol) of triethylamine were dissolved in 50 ml of methylene chloride, and 0.75 ml (9.7 mmol) of methanesulfonyl chloride was added to this solution, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate and water, and dried. The solvent was distilled off.

45     To a solution of 2.2 g of the residue and 0.75 g (6.8 mmol) of 4-mercaptopyridine in 30 ml of methylene chloride, 1.14 ml (8.2 mmol) of triethylamine was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate and water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 1) to give 0.17 g of the desired compound (6.17% yield, yellow oil).

NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.02-3.15 (2H, m), 3.50-3.68 (2H, m), 4.68 and 4.74 (2H, s)†, 7.08 (2H, dd, J=1.6, 4.8 Hz), 7.19-7.24 (2H, m), 7.35-7.42 (3H, m), 8.38 (2H, bd, J=5.6 Hz). †: The peak is split due to the rotational isomers.

50     IR (neat) cm<sup>-1</sup>: 3040, 2950, 1690, 1580, 805, 705.

##### b) Process by way of bromide

55     To a solution of 2.47 g (10.0 mmol) of N-benzyl N trifluoroacetyl-aminoethanol and 3.65 g (11.0 mmol) of carbon tetrabromide in 80 ml of methylene chloride, 2.89 g (11.0 mmol) of triphenylphosphine was added, and the mixture was stirred at room temperature for 16 hours. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 1) to give 2.69 g of the desired compound (86.7% yield, colorless oil).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.35 and 3.45 (2H, t,  $J=7.8, 6.6$  Hz) $\ddagger$ , 3.69 and 3.47 (2H, t,  $J=6.4$  Hz) $\ddagger$ , 4.73 and 4.76 (2H, s) $\ddagger$ , 7.19-7.25 (2H, m), 7.35-7.42 (3H, m).  $\ddagger$ : The peak is split due to the rotational isomers.

IR (neat)  $\text{cm}^{-1}$ : 3040, 2950, 1685, 1205, 750, 700.

To a solution of 0.11 g (1.0 mmol) of 4-mercaptopyridine and 0.15 ml (1.1 mmol) of DBU in 5 ml of DMF, 0.34 g (1.1 mmol) of the above bromide was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was washed with water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 1) to give 0.12 g of the desired compound (35.0% yield, yellow oil).

#### Example 120

Synthesis of 4-[2-(N-benzyl-N-benzoylamino)ethylthio]pyridine

##### a) Process by way of chloride

N-Benzyl-N-benzoylaminoethanol [2.0 g (8.1 mmol)] and 1.35 ml (9.7 mmol) of triethylamine were dissolved in 50 ml of methylene chloride, and 0.75 ml (9.7 mmol) of methanesulfonyl chloride was added to this solution, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate and water, and dried. The solvent was distilled off.

To a solution of 2.42 g of the residue and 0.90 g (8.1 mmol) of 4-mercaptopyridine in 20 ml of ethanol, 1.36 ml (9.7 mmol) of triethylamine was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 64 hours. The solvent was distilled off and the residue was dissolved in chloroform. The solution was washed with water and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 1) to give 1.04 g of the desired compound (36.8% yield, yellow oil).

Anal. for  $\text{C}_{21}\text{H}_{20}\text{N}_2\text{OS}$ .

Calcd.: C; 72.38, H; 5.78, N; 8.04.

Found: C; 72.10, H; 5.99, N; 7.74.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.27 (2H, bm), 3.69 (2H, bm), 4.56-4.83 (2H, bm), 7.16-7.46 (7H, bm), 8.32-8.44 (2H, bm).

IR (neat)  $\text{cm}^{-1}$ : 3030, 1640, 1580, 815, 700.

##### b) Process by way of bromide

To a solution of 2.55 g (10.0 mmol) of N-benzyl-N-benzoylaminoethanol and 3.65 g (11.0 mmol) of carbon tetrabromide in 80 ml of methylene chloride, 2.89 g (11.0 mmol) of triphenylphosphine was added, and the mixture was stirred at room temperature for 16 hours. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 1) to give 0.50 g of the desired compound (15.7% yield, colorless oil).

#### Example 121

Synthesis of 4-(2-picolinylaminoethylthio)pyridine

To a solution of 1.42 g (5.0 mmol) of 4-(2-phthalimidoethylthio)pyridine in 50 ml of ethanol, 0.73 ml (15.0 mmol) of hydrazine monohydrate was added, and the mixture was stirred at room temperature for 3 hours. The solvent was distilled off and the residue was dissolved in chloroform. The precipitate was filtered and the filtrate was concentrated. The resulting residue was used for the subsequent reaction.

To a solution of the above residue and 3.14 ml (22.5 mmol) of triethylamine in 50 ml of methylene chloride, 1.78 g (10.0 mmol) of picolinyl chloride hydrochloride was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate and water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 1 to ethyl acetate) to give 0.67 g of the desired compound (51.6% yield, yellow crystals).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.28 (2H, t,  $J=6.6$  Hz), 3.76 and 3.79 (2H, t,  $J=7.2$  Hz) $\ddagger$ , 7.27 (2H, dd,  $J=1.6, 4.6$  Hz), 7.45 (1H, ddd,  $J=1.4, 4.8, 7.8$  Hz), 7.87 (1H, ddd,  $J=1.8, 7.6, 7.6$  Hz), 8.20 (1H, ddd,  $J=1.2, 1.4, 7.8$  Hz), 8.41 (2H, dd,  $J=1.6, 4.6$  Hz), 8.43 (1H, bs), 8.51-8.62 (1H, m).  $\ddagger$ : The peak is split due to the rotational isomers.

IR (KBr)  $\text{cm}^{-1}$ : 3300, 3050, 2950, 1670.

#### Example 122

##### 5 Synthesis of 4-(2-thenoylaminoethylthio)pyridine

To a solution of 1.42 g (5.0 mmol) of 4-(2-phthalimidoethylthio)pyridine in 50 ml of ethanol, 0.73 ml (15.0 mmol) of hydrazine monohydrate was added, and the mixture was stirred at room temperature for 3 hours. The solvent was distilled off and the residue was dissolved in chloroform. The precipitate was filtered and the filtrate  
10 was concentrated. The resulting residue was used for the subsequent reaction.

To a solution of the above residue and 3.14 ml (22.5 mmol) of triethylamine in 50 ml of methylene chloride, 1.07 ml (10.0 mmol) of thenoyl chloride was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate and water, and dried. The solvent was distilled off and the residue was purified by column chromatography  
15 (eluent: ethyl acetate/hexane = 1 : 1 to ethyl acetate) to give 0.79 g of the desired compound (60.0% yield, yellow crystals).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.27 (2H, t,  $J=6.6$  Hz), 3.70 and 3.74 (2H, t,  $J=6.8, 6.4$  Hz) $\ddagger$ , 6.46 (1H, bs), 7.08 (1H, dd,  $J=3.9, 5.0$  Hz), 7.24 (2H, dd,  $J=1.8, 4.6$  Hz), 7.47-7.52 (2H, m), 8.41 (2H, dd,  $J=1.8, 4.6$  Hz).  $\ddagger$ : The peak is split due to the rotational isomers.

20 IR (KBr)  $\text{cm}^{-1}$ : 3180, 3005, 1640, 1580, 810, 700.

#### Example 123

##### 25 Synthesis of 4-[2-(thianaphthene-2-carbonylamino)ethylthio]pyridine

To a solution of 2.82 g (10.0 mmol) of 4-(2-phthalimidoethylthio)pyridine in 50 ml of ethanol, 1.46 ml (30.0 mmol) of hydrazine monohydrate was added, and the mixture was stirred at room temperature for 3 hours. The solvent was distilled off and the residue was dissolved in chloroform. The precipitate was filtered and the filtrate  
30 was concentrated. The resulting residue was used for the subsequent reaction.

To a solution of the above residue and 2.79 ml (20.0 mmol) of triethylamine in 50 ml of methylene chloride, 1.96 g (10.0 mmol) of thianaphthene-2-carbonyl chloride was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate and water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 1) to give 0.419 g of the desired compound (13.3% yield,  
35 yellow crystals).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.29 (2H, t,  $J=6.8$  Hz), 3.27 and 3.77 (2H, t,  $J=7.0, 6.4$  Hz) $\ddagger$ , 6.78 (1H, bs), 7.24 (1H, dd,  $J=1.6, 4.6$  Hz), 7.39-7.45 (2H, m), 7.77 (1H, s), 7.81-7.88 (2H, m), 8.41 (2H, dd,  $J=1.8, 4.6$  Hz).  $\ddagger$ : The peak is split due to the rotational isomers.

40 IR (KBr)  $\text{cm}^{-1}$ : 3220, 3050, 1650, 1630, 805.

#### Example 124

##### Synthesis of 4-[3-(2-pyrazinecarbonylamino)propylthio]pyridine

45 To a solution of 1.00 g (8.06 mmol) of 2-pyrazinecarboxylic acid and 1.21 g (10.5 mmol) of N-hydroxysuccinimide in 70 ml of methylenechloride, 1.85 g (9.67 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC) was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 1 hour. Further, 1.94 g (8.06 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride was added, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate and water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 0.751 g of the desired compound (34.0% yield, colorless  
50 powder).

Anal. for  $\text{C}_{13}\text{H}_{14}\text{N}_4\text{OS}$ .

Calcd.: C; 56.91, H; 5.14, N; 20.42.

55 Found: C; 56.84, H; 5.25, N; 20.22.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.08 (2H, quint.,  $J=6.8$  Hz), 3.09 (2H, t,  $J=7.2$  Hz), 3.65 and 3.68 (2H, t,  $J=6.6$  Hz) $\ddagger$ , 7.13 (2H, dd,  $J=1.6, 4.6$  Hz), 7.94 (1H, bs), 8.40 (2H, bd,  $J=6.0$  Hz), 8.53 (1H, dd,  $J=1.4, 2.4$  Hz), 8.78 (1H, d,  $J=2.4$  Hz), 9.42 (1H, d,  $J=1.4$  Hz).  $\ddagger$ : The peak is split due to the rotational isomers.

IR (KBr)  $\text{cm}^{-1}$ : 3380, 3030, 1660, 1580, 800, 710.

#### Example 125

##### 5 Synthesis of 4-[3-(2-picolinoylamino)propyloxy]pyridine

The desired compound was synthesized in the same manner as described in Example 86.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.18 (2H, m), 3.70 (2H, m), 4.16 (2H, t,  $J=6$  Hz), 6.85 (2H, dd,  $J=4.8, 1.6$  Hz), 7.44 (1H, m), 7.86 (1H, m), 8.20 (1H, m), 8.34 (1H, br), 8.43 (2H, dd,  $J=4.8, 1.6$  Hz), 8.56 (1H, m).

10 IR (neat)  $\text{cm}^{-1}$ : 1670, 1595, 1570, 1530.

#### Example 126

##### 15 Synthesis of 4-[3-(2-picolinoylamino)propyloxy]pyridine dihydrochloride

The desired compound was synthesized in the same manner as described in Example 113, mp. 156-168°C.

Anal. for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_2 \cdot 2\text{HCl} \cdot 0.5\text{H}_2\text{O}$ ,

Calcd.: C; 49.57, H; 5.35, N; 12.39, Cl; 20.90.

Found: C; 49.86, H; 5.28, N; 12.62, Cl; 21.06.

20 NMR (200 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 2.09 (2H, m), 3.49 (2H, m), 4.40 (2H, m), 7.55 (2H, d,  $J=7.2$  Hz), 7.62 (1H, m), 7.98-8.08 (2H, m), 8.66 (1H, m), 8.76 (2H, d,  $J=7.2$  Hz), 9.03 (1H, br).

IR (KBr)  $\text{cm}^{-1}$ : 3420, 1685, 1640, 1605, 1510.

#### Example 127

##### 25 Synthesis of 4-[4-(benzoylamino)butylthio]pyridine

##### i) Synthesis of 4-(4-aminobutylthio)pyridine

30 To a suspension of 12.50 g (40 mmol) of 4-(4-phthalimidobutylthio)pyridine in 200 ml of ethanol, 5.82 ml (120 mmol) of hydrazine monohydrate was added, and the mixture was stirred at room temperature for 4 hours. Then, 200 ml of ethyl acetate was added, and the insoluble material was filtered off. The volatile components were distilled off and chloroform was added to the residue. The mixture was washed with saturated saline and dried over potassium carbonate. The solvent was distilled off and 7.30 g of the desired compound were obtained

35 (quantitative yield, yellow oil).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.54-1.90 (4H, m), 2.55 (2H, br), 2.76 (2H, t,  $J=6.8$  Hz), 3.00 (2H, m), 7.08 (2H, dd,  $J=4.8, 1.6$  Hz), 8.35 (2H, dd,  $J=4.8, 1.6$  Hz).

##### ii) Synthesis of 4-[4-(benzoylamino)butylthio]pyridine

40 To a solution of 1.00 g (5.49 mmol) of 4-(4-aminobutylthio)pyridine and 0.92 ml (6.60 mmol) of triethylamine in 30 ml of methylene chloride, 0.67 ml (5.77 mmol) of benzoyl chloride was added with stirring under ice-cooling and the mixture was stirred at room temperature for 13 hours. The mixture was washed with saturated aqueous sodium bicarbonate and saturated saline, and dried over anhydrous magnesium sulfate. The solvent was dis-

45 tilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 0.54 g of the desired compound (34.4% yield, colorless crystals), mp. 75-77°C.

Anal. for  $\text{C}_{18}\text{H}_{18}\text{N}_2\text{OS}$ ,

Calcd.: C; 67.10, H; 6.33, N; 9.78.

Found: C; 67.36, H; 6.19, N; 9.80.

50 NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.82 (4H, m), 3.05 (2H, m), 3.52 (2H, m), 6.19 (1H, br), 7.12 (2H, m), 7.36-7.56 (3H, m), 7.70-7.80 (2H, m), 8.38 (2H, m).

IR (KBr)  $\text{cm}^{-1}$ : 1640, 1575, 1530.

#### Example 128

##### 55 Synthesis of 4-[4-(thianaphthene-2-carbonylamino)butylthio]pyridine

The desired compound was synthesized in the same manner as described in Example 86, mp. 90-92°C.

Anal. for  $C_{18}H_{18}N_2OS$ .

Calcd.: C; 63.13, H; 5.30, N; 8.18.

Found: C; 63.27, H; 5.30, N; 8.21.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.82 (4H, m), 3.02 (2H, m), 3.52 (2H, m), 6.48 (1H, br), 7.10 (2H, dd,  $J=4.8$ , 1.6 Hz), 7.32-7.46 (2H, m), 7.73-7.86 (3H, m), 8.36 (2H, m).

IR (KBr)  $cm^{-1}$ : 1635, 1575, 1540.

#### Example 129

##### 10 Synthesis of 4-[4-(2-thenonylamino)butylthio]pyridine

The desired compound was synthesized in the same manner as described in Example 86, mp. 89-91°C.

Anal. for  $C_{14}H_{16}N_2OS_2$ .

Calcd.: C; 57.50, H; 5.51, N; 9.58.

15 Found: C; 57.61, H; 5.30, N; 9.62.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.80 (4H, m), 3.03 (2H, m), 3.48 (2H, m), 6.23 (1H, br), 7.07 (1H, dd,  $J=5$ , 1.8 Hz), 7.11 (2H, dd,  $J=4.8$ , 1.6 Hz), 7.44-7.52 (2H, m), 8.37 (2H, m).

IR (KBr)  $cm^{-1}$ : 1630, 1580, 1540.

#### 20 Example 130

##### Synthesis of 4-[4-(2-picolinoylamino)butylthio]pyridine

The desired compound was synthesized in the same manner as described in Example 86.

25 NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.83 (4H, m), 3.04 (2H, m), 3.55 (2H, m), 7.11 (2H, dd,  $J=4.6$ , 1.8 Hz), 7.44 (1H, m), 7.87 (1H, m), 8.13 (1H, br), 8.21 (1H, m), 8.36 (2H, dd,  $J=4.6$ , 1.6 Hz), 8.54 (1H, m).

IR (neat)  $cm^{-1}$ : 1670, 1575, 1530.

#### Example 131

30

##### Synthesis of 4-(4-benzoylpiperidylthio)pyridine

The desired compound was synthesized in the same manner as described in Example 13, mp. 123-124°C.

Anal. for  $C_{17}H_{18}N_2OS$ .

35 Calcd.: C; 68.43, H; 6.08, N; 9.39.

Found: C; 68.71, H; 6.10, N; 9.42.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.72 (2H, m), 2.10 (2H, m), 3.28 (2H, m), 3.64 (1H, m), 7.19 (2H, dd,  $J=4.6$ , 1.6 Hz), 7.41 (5H, m), 8.43 (2H, dd,  $J=4.6$ , 1.6 Hz).

IR (KBr)  $cm^{-1}$ : 1625, 1575.

40

#### Example 132

##### Synthesis of 4-[4-(2-thenoyl)piperidylthio]pyridine

45 The desired compound was synthesized in the same manner as described in Example 13.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.76 (2H, m), 2.15 (2H, m), 3.40 (2H, m), 3.67 (1H, m), 4.27 (2H, m), 7.05 (1H, dd,  $J=5$ , 3.6 Hz), 7.20 (2H, dd,  $J=4.6$ , 1.6 Hz), 7.29 (1H, dd,  $J=3.6$ , 1.2 Hz), 7.46 (1H, dd,  $J=5$ , 1.2 Hz), 8.44 (2H, dd,  $J=4.6$ , 1.6 Hz).

IR (KBr)  $cm^{-1}$ : 1600, 1575.

50

#### Example 133

##### Synthesis of 4-[4-(thianaphthene-2-carbonyl)piperidylthio]pyridine

55 The desired compound was synthesized in the same manner as described in Example 13, mp. 146-147°C.

Anal. for  $C_{19}H_{18}N_2OS_2$ .

Calcd.: C; 64.38, H; 5.12, N; 7.90.

Found: C; 64.34, H; 4.89, N; 7.94.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.80 (2H, m), 2.17 (2H, m), 3.44 (2H, m), 3.69 (1H, m), 4.29 (1H, m), 7.22 (2H, dd,  $J=4.6, 1.6$  Hz), 7.25-7.51 (3H, m), 7.75-7.92 (2H, m), 8.45 (2H, dd,  $J=4.6, 1.6$  Hz).  
IR (KBr)  $\text{cm}^{-1}$ : 1615, 1575, 1520.

5 Example 134

Synthesis of 4-[4-(2-picolinyl)piperidylthio]pyridine

The desired compound was synthesized in the same manner as described in Example 13.

10 NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.68-2.31 (4H, m), 3.36 (2H, m), 3.68 (1H, m), 3.98 (1H, m), 4.46 (1H, m), 7.21 (2H, dd,  $J=4.8, 1.6$  Hz), 7.37 (1H, m), 7.66 (1H, m), 7.82 (1H, m), 8.44 (2H, dd,  $J=4.8, 1.6$  Hz), 8.59 (1H, m).

IR (KBr)  $\text{cm}^{-1}$ : 1625, 1585, 1575, 1565.

15 Example 135

Synthesis of 4-(4-pivaloylpiperidylthio)pyridine

The desired compound was synthesized in the same manner as described in Example 13.

20 NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.29 (9H, s), 1.60 (2H, m), 2.11 (2H, m), 3.22 (2H, m), 3.61 (1H, m), 4.23 (2H, m), 7.17 (2H, dd,  $J=4.6, 1.6$  Hz), 8.44 (2H, dd,  $J=4.6, 1.6$  Hz).

IR (neat)  $\text{cm}^{-1}$ : 1630, 1575.

Example 136

25

Synthesis of 4-(4-isobutyrylpiperidylthio)pyridine

The desired compound was synthesized in the same manner as described in Example 13.

30 NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.13 (6H, d,  $J=6.8$  Hz), 1.65 (2H, m), 2.10 (2H, m), 2.80 (1H, heptet,  $J=6.8$  Hz), 3.10 (1H, m), 3.30 (1H, m), 3.60 (1H, m), 3.90 (1H, m), 4.33 (1H, m), 7.17 (2H, dd,  $J=4.6, 1.6$  Hz), 8.44 (2H, dd,  $J=4.6, 1.6$  Hz).

IR (neat)  $\text{cm}^{-1}$ : 1640, 1575.

Example 137

35

Synthesis of 2-[3-(2-hydroxybenzoylamino)propylthio]pyridine

To a solution of 5.97 g (20 mmol) of 2-(3-phthalimido)propylthiopyridine in 100 ml of ethanol, 2.91 ml (60 mmol) of hydrazine monohydrate was added, and the mixture was heated under reflux for 1 hour. After cooling, 40 100 ml of methylene chloride was added and the insoluble material was filtered off. The solvent was distilled off from the filtrate. To the residue, 100 ml of methylene chloride and 4.18 ml (30 mmol) of triethylamine were added, and 4.77 g (24 mmol) of O-acetylsalicyloyl chloride was added with stirring under ice-cooling and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off, and 60 ml of ethanol and 40 45 ml of 1N-NaOH was added to the residue. The mixture was stirred for 1 hour. Then, 40 ml of 1N-HCl was added and ethanol was distilled off. The residue was extracted with chloroform and the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified column chromatography (eluent: ethyl acetate/n-hexane = 1 : 1) to give 4.86 g (84.2% yield, colorless oil).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.00 (2H, m), 3.35 (2H, m), 3.59 (2H, m), 6.85-7.08 (3H, m), 7.25 (1H, d,  $J=8$  Hz), 7.35-7.66 (3H, m), 8.02 (1H, br), 8.42 (1H, m).

50 IR (neat)  $\text{cm}^{-1}$ : 3355, 1640, 1595, 1580, 1545, 1530.

Example 138

Synthesis of 4-(3-picolinoylaminomethylthio)pyridine

55

To a mixture of 1.11 g (10 mmol) of 4-mercaptopyridine and 1.52 g (10 mmol) of N-(hydroxymethyl)nicotinamide, 30 ml of trifluoroacetic acid was added, and the mixture was stirred at room temperature for 1 hour. The solvent was distilled off and 30 ml of ethanol was added to the residue. The solvent was distilled off and



water was added to the residue. The mixture was neutralized with saturated aqueous sodium bicarbonate, followed by extraction with chloroform. After washing with saturated saline, the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/ethanol = 5 : 1) to give 390 mg of the desired compound (15.9% yield, yellow solid).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.06 (2H, d,  $J=6$  Hz), 7.27 (2H, dd,  $J=4.6, 1.6$  Hz), 7.37 (1H, m), 7.71 (1H, br), 8.14 (1H, m), 8.36 (2H, dd,  $J=4.6, 1.6$  Hz), 8.70 (1H, dd,  $J=4.8, 1.6$  Hz), 8.97 (1H, m).

IR (KBr)  $\text{cm}^{-1}$ : 1655, 1620, 1585, 1540.

#### Example 139

##### Synthesis of 3-[3-(4-pyridylthio)propyl]-2H-1,3-benzoxadine-2,4(3H)-dione

To a solution of 1.153 g (4.0 mmol) of 4-[3-(2-hydroxybenzoylamino)]propylthiopyridine in 30 ml of dry tetrahydrofuran, 1.30 g (10.0 mmol) of 1,1'-carbonyl-diimidazole was added, and the mixture was stirred at room temperature for 3 hours. The solvent was distilled off and chloroform was added to the residue. The mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 1.14 g of the desired compound (90.7% yield, colorless crystals), mp. 101.5-102°C.

Anal. for  $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$ .

Calcd.: C; 61.13, H; 4.49, N; 8.91.

Found: C; 61.20, H; 4.25, N; 8.98.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.16 (2H, m), 3.08 (2H, t,  $J=7.4$  Hz), 4.22 (2H, t,  $J=7$  Hz), 7.15 (2H, dd,  $J=4.8, 1.6$  Hz), 7.25-7.44 (2H, m), 7.73 (1H, m), 8.09 (1H, dd,  $J=8, 1.8$  Hz), 8.40 (2H, dd,  $J=4.8, 1.6$  Hz).

IR (KBr)  $\text{cm}^{-1}$ : 1760, 1695, 1620, 1580.

#### Example 140

##### Synthesis of 5,5-dimethyl-3-[4-(4-pyridylthio)butyl]hydantoin

To a solution of 2.56 g (20 mmol) of 5,5-dimethyl hydantoin and 4.03 g (20 mmol) of 4-(4-chlorobutylthio)pyridine in 20 ml of N,N-dimethylformamide, 3.00 ml (20 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at room temperature for 43 hours, followed by further stirring at 70°C for 10 hours. Ethyl acetate was added to the reaction mixture, and the mixture was washed three times with water and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/ethanol = 10 : 1) to give 3.33 g of the desired compound (56.8% yield, colorless crystals).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.42 (6H, s), 1.77 (4H, m), 3.02 (2H, t,  $J=7$  Hz), 3.54 (2H, t,  $J=6.6$  Hz), 6.93 (1H, br), 7.11 (2H, dd,  $J=4.8, 1.6$  Hz), 8.37 (2H, dd,  $J=4.8, 1.6$  Hz).

IR (neat)  $\text{cm}^{-1}$ : 3300, 1775, 1710, 1580.

#### Example 141

##### Synthesis of 3-[3-(4-pyridylthio)propyl]-2H-1,3-benzoxadine-2-thion-4(3H)-one

To a solution of 1.442 g (5.0 mmol) of 4-[3-(2-hydroxybenzoylamino)]propylthiopyridine in 30 ml of dry tetrahydrofuran, 1.78 g (10.0 mmol) of 1,1'-thiocarbonyl-diimidazole was added, and the mixture was stirred at room temperature for 6 hours. The solvent was distilled off and chloroform was added to the residue. The mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/n-hexane = 2 : 1) to give 1.57 g of the desired compound (95.0% yield, colorless crystals), mp. 118.5-119°C.

Anal. for  $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2$ .

Calcd.: C; 58.16, H; 4.27, N; 8.48.

Found: C; 58.00, H; 4.28, N; 8.41.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.26 (2H, m), 3.11 (2H, t,  $J=7.4$  Hz), 4.62 (2H, m), 7.15 (2H, dd,  $J=4.8, 1.6$  Hz), 7.32-7.46 (2H, m), 7.75 (1H, m), 8.07 (1H, dd,  $J=7.8, 1.8$  Hz), 8.40 (2H, dd,  $J=4.8, 1.6$  Hz).

IR (KBr)  $\text{cm}^{-1}$ : 1710, 1620, 1595, 1580.

Example 142

## Synthesis of 1-methyl-3-[4-(4-pyridylthio)butyl]hydantoin

5 The desired compound was synthesized in the same manner as described in Example 140.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.77 (4H, m), 3.00 (3H, s), 3.02 (2H, t, J=7 Hz), 3.55 (2H, t, J=6.6 Hz), 3.85 (2H, s), 7.12 (2H, dd, J=4.8, 1.6 Hz), 8.39 (2H, dd, J=4.8, 1.6 Hz).

IR (neat)  $\text{cm}^{-1}$ : 1770, 1710, 1575.

10 Example 143

## Synthesis of 4-(4-succinimidobutylthio)pyridine

The desired compound was synthesized in the same manner as described in Example 140, mp. 80-81°C.

15 Anal. for  $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ .

Calcd.: C; 59.07, H; 6.10, N; 10.60.

Found: C; 59.36, H; 6.04, N; 10.63.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.73 (4H, m), 2.70 (4H, s), 3.00 (2H, t, J=6.8 Hz), 3.55 (2H, t, J=6.8 Hz), 7.09 (2H, dd, J=4.6, 1.6 Hz), 8.39 (2H, dd, J=4.6, 1.6 Hz).

20 IR (KBr)  $\text{cm}^{-1}$ : 1770, 1710, 1580.

Example 144

## Synthesis of 4-(2-benzoylaminoethylthio)pyridine

25

To a solution of 1.99 g (7.0 mmol) of 4-(2-phthalimidoethylthio)pyridine in 70 ml of ethanol, 1.02 ml (21.0 mmol) of hydrazine monohydrate was added, and the mixture was stirred at room temperature for 4 hours. The solvent was distilled off and the residue was dissolved in chloroform. The precipitate was filtered and the filtrate was concentrated. The resulting residue was used for the subsequent reaction.

30

To a solution of the above residue and 1.25 ml (9.0 mmol) of triethylamine in 50 ml of methylene chloride, 0.89 ml (7.7 mmol) of benzoyl chloride was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with saturated aqueous sodium bicarbonate and water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 3) to give 0.50 g of the desired compound (27.7% yield, yellow oil).

35

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.29 (2H, t, J=6.6 Hz), 3.73 and 3.76 (2H, t, J=6.2, 6.6 Hz) $\ddagger$ , 6.67 (1H, bs), 7.25 (2H, dd, J=1.6, 4.6 Hz), 7.43-7.52 (3H, m), 7.72-7.77 (2H, m), 8.42 (2H, bd, J=6.0 Hz).  $\ddagger$ : The peak is split due to the rotational isomers.

IR (neat)  $\text{cm}^{-1}$ : 3300, 3055, 2930, 1640, 1580, 1310, 800, 710.

40

Example 145

## Synthesis of 4-(2, 2-dimethyl-3-phthalimidopropylthio)pyridine

45

To a solution of 0.56 g (5.0 mmol) of 4-mercaptopyridine and 1.48 g (5.0 mmol) of (N-3-bromo-2,2-dimethyl propyl)phthalimide in 20 ml of dimethylformamide, 0.75 ml (5.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 8 hours. Water was added, and the mixture was extracted with ethylacetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate) to give 12.0 g of the desired compound (71.6% yield, colorless columns).

50

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.13 (6H, s), 3.03 (2H, s), 3.70 (2H, s), 7.17 (2H, dd, J=1.6, 4.6 Hz), 7.72-7.92 (4H, m), 8.38 (2H, dd, J=1.6, 4.6 Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3030, 2960, 1715, 1580, 800, 720.

Example 146

55

## Synthesis of 3-[4-(4-pyridylthio)butyl]quinazolin-2,4(1H,3H)-dione

The desired compound was synthesized in the same manner as described in Example 140.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.66-2.03 (4H, m), 3.07 (2H, t,  $J=7$  Hz), 4.15 (2H, t,  $J=7$  Hz), 7.06-7.16 (3H, m), 7.25 (1H, m), 7.61 (1H, m), 8.14 (1H, m), 8.38 (2H, m), 10.02 (1H, br).  
IR (KBr)  $\text{cm}^{-1}$ : 1710, 1660.

#### 5     Example 147

Synthesis of 1,3-bis[4-(4-pyridylthio)butyl]quinazolin-2,4-(1H,3H)-dione

The desired compound was synthesized in the same manner as described in Example 140.

10     NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.70-2.07 (8H, m), 2.97-3.14 (4H, m), 4.07-4.25 (4H, m), 7.05-7.14 (4H, m), 7.17 (1H, d,  $J=8.4$  Hz), 7.27 (1H, m), 7.69 (1H, m), 8.25 (1H, dd,  $J=7.8, 1.6$  Hz), 8.31-8.45 (4H, m).  
IR (neat)  $\text{cm}^{-1}$ : 1700, 1660, 1610, 1575.

#### Example 148

15

Synthesis of 4-[4-(2-hydroxymethylbenzoyl)aminobutyloxy]pyridine

The desired compound was synthesized in the same manner as described in Example 100.

20     NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.71-2.03 (4H, m), 3.56 (2H, m), 4.09 (2H, t,  $J=5.8$  Hz), 4.62 (2H, s), 6.54 (1H, br), 6.80 (2H, dd,  $J=4.8, 1.6$  Hz), 7.37-7.58 (4H, m), 8.42 (2H, dd,  $J=4.8, 1.6$  Hz).  
IR (KBr)  $\text{cm}^{-1}$ : 3290, 3090, 3070, 1650, 1605, 1570.

#### Example 149

25

Synthesis of 3-[4-(4-pyridylthio)butyl]-1-benzylquinazolin-2,4-(1H,3H)-dione

The desired compound was synthesized in the same manner as described in Example 140.

30     NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.72-2.05 (4H, m), 3.06 (2H, t,  $J=7.2$  Hz), 4.21 (2H, t,  $J=7$  Hz), 5.38 (2H, s), 7.05-7.40 (9H, m), 7.55 (1H, m), 8.24 (1H, dd,  $J=7.8, 1.6$  Hz), 8.36 (2H, dd,  $J=6.8, 1.6$  Hz).  
IR (KBr)  $\text{cm}^{-1}$ : 1700, 1660, 1610, 1575, 1485.

#### Example 150

35

Synthesis of 4-[4-(5-benzylidene-2,4-thiazolidinedione)butylthio]pyridine

i) Synthesis of 5-benzylidene-2,4-thiazolidinedione

40     To a solution of 20 g (171 mmol) of 2,4-thiazolidinedione and 17.4 ml (171 mmol) of benzaldehyde in 350 ml of ethanol, 1.68 ml (17.1 mmol) of piperidine was added, and the mixture was heated under reflux for 5 hours. After cooling, the precipitated crystals were filtered and washed with cooled ethanol to give 31.67 g of the desired compound (90.4% yield, pale yellow crystals).

Anal. for  $\text{C}_{10}\text{H}_7\text{NO}_2\text{S}$ ,

Calcd.: C; 58.52, H; 3.44, N; 6.82.

Found: C; 58.74, H; 3.42, N; 6.82.

45

NMR (200 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 7.48-7.63 (5H, m), 7.81 (1H, s), 12.40 (1H, bs).

IR (KBr)  $\text{cm}^{-1}$ : 3140, 3020, 2780, 1740, 1690, 1605.

ii) Synthesis of 4-[4-(5-benzylidene-2,4-thiazolidinedione)butylthio]pyridine

50

To a solution of 2.0 g (9.74 mmol) of 5-benzylidene-2,4-thiazolidinedione and 1.96 g (9.74 mmol) of 4-(4-chlorobutylthio)pyridine in 80 ml of dimethylformamide, 1.46 ml (9.74 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 2 : 1) to give

55

2.40 g of the desired compound (66.6% yield, pale yellow crystals).

Anal. for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2\text{S}_2$ ,

Calcd.: C; 61.60, H; 4.90, N; 7.56.

Found: C; 61.74, H; 5.04, N; 7.41.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.68-1.96 (4H, m), 3.03 (2H, t,  $J=7.0$  Hz), 3.81 (2H, t,  $J=6.8$  Hz), 7.11 (2H, dd,  $J=1.6, 4.8$  Hz), 7.45-7.54 (5H, m), 7.81 (1H, s), 8.39 (2H, dd,  $J=1.6, 4.8$  Hz).  
 IR (KBr)  $\text{cm}^{-1}$ : 3040, 2950, 1745, 1680, 1615, 1580, 1130, 800, 770, 695.

### 5 Example 151

Synthesis of 4-[4-[5-(4-chlorobenzylidene)-2,4-thiazolidinedione]butylthio]pyridine

#### i) Synthesis of 5-(4-chlorobenzylidene)-2,4-thiazolidinedione

10 To a solution of 20 g (171 mmol) of 2,4-thiazolidinedione and 17.4 ml (171 mmol) of 4-chlorobenzaldehyde in 350 ml of ethanol, 1.68 ml (17.1 mmol) of piperidine was added, and the mixture was heated under reflux for 5 hours. After cooling, the precipitated crystals were filtered and washed with cooled ethanol to give 17.75 g of the desired compound (43.4% yield, pale yellow crystals).

15 Anal. for  $\text{C}_{10}\text{H}_6\text{NO}_2\text{S}$ ,

Calcd.: C; 50.11, H; 2.52, N; 5.84.

Found: C; 50.02, H; 2.52, N; 5.91.

NMR (200 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 7.61 (4H, s), 7.79 (1H, s).

IR (KBr)  $\text{cm}^{-1}$ : 3150, 3050, 2760, 1750, 1720, 1610.

#### 20 ii) 4-[4-[5-(4-chlorobenzylidene)-2,4-thiazolidinedione]butylthio]pyridine

To a solution of 2.0 g (8.34 mmol) of 5-(4-chlorobenzylidene)-2,4-thiazolidinedione and 1.68 g (8.34 mmol) of 4-(4-chlorobutylthio)pyridine in 80 ml of dimethylformamide, 1.24 ml (8.34 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 2 : 1) to give 2.08 g of the desired compound (61.5% yield, pale yellow crystals).

Anal. for  $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_2\text{S}_2\text{Cl}$ ,

30 Calcd.: C; 56.36, H; 4.23, N; 6.92.

Found: C; 56.27, H; 4.23, N; 6.77.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.64-1.95 (4H, m), 3.02 (2H, t,  $J=7.2$  Hz), 3.80 (2H, t,  $J=6.8$  Hz), 7.10 (2H, dd,  $J=1.8, 4.8$  Hz), 7.45 (4H, s), 7.84 (1H, s), 8.38 (2H, dd,  $J=1.6, 4.8$  Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3040, 2950, 1740, 1685, 1610, 1580, 1345, 810, 710.

### 35 Example 152

Synthesis of 4-[4-[5-(4-methoxybenzylidene)-2,4-thiazolidinedione]butylthio]pyridine

40 To a solution of 20 g (171 mmol) of 2,4-thiazolidinedione and 20.6 ml (171 mmol) of anisaldehyde in 350 ml of ethanol, 1.68 ml (17.1 mmol) of piperidine was added, and the mixture was heated under reflux for 5 hours. After cooling, the precipitated crystals were filtered and washed with cooled ethanol to give 30.75 g of the desired compound (76.5% yield, pale yellow crystals).

Anal. for  $\text{C}_{11}\text{H}_9\text{NO}_3\text{S}$ ,

45 Calcd.: C; 56.16, H; 3.86, N; 5.95.

Found: C; 56.43, H; 4.04, N; 6.18.

NMR (200 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 3.83 (3H, s), 7.11 (2H, d,  $J=8.3$  Hz), 7.55 (2H, d,  $J=7.4$  Hz), 7.79 (1H, s).

IR (KBr)  $\text{cm}^{-1}$ : 3230, 1745, 1690, 1590, 1285, 695.

#### 50 ii) Synthesis of 4-[4-[5-(4-methoxybenzylidene)-2,4-thiazolidinedione]butylthio]pyridine

To a solution of 2.0 g (8.50 mmol) of 5-(4-methoxybenzylidene)-2,4-thiazolidinedione and 1.71 g (8.50 mmol) of 4-(4-chlorobutylthio)pyridine in 80 ml of dimethylformamide, 1.27 ml (8.50 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 2 : 1) to give 2.35 g of the desired compound (69.0% yield, pale yellow crystals).

Anal. for  $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3\text{S}_2$ ,

Calcd.: C; 59.98, H; 5.03, N; 6.99.

Found: C; 66.06, H; 5.19, N; 6.92.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.68-1.94 (4H, m), 3.02 (2H, t,  $J=7.0$  Hz), 3.79 (2H, t,  $J=6.8$  Hz), 3.87 (3H, s), 6.99 (2H, d,  $J=8.8$  Hz), 7.09 (2H, dd,  $J=1.8, 4.8$  Hz), 7.47 (2H, d,  $J=9.0$  Hz), 7.85 (1H, s), 8.38 (2H, dd,  $J=1.4, 4.4$  Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3040, 2950, 1750, 1690, 1600, 1580, 825, 805, 740, 715.

### Example 153

#### 10 Synthesis of 4-[4-(5-benzylidenerhodanine)butylthio]pyridine

##### i) Synthesis of 5-benzylidenerhodanine

To a solution of 10 g (75.1 mmol) of rhodanine and 7.63 ml (75.1 mmol) of benzaldehyde in 150 ml of ethanol, 0.74 ml (7.5 mmol) of piperidine was added, and the mixture was heated under reflux for 5 hours. After cooling, the precipitated crystals were filtered and washed with cooled ethanol to give 11.07 g of the desired compound (66.6% yield, pale yellow crystals).

Anal. for  $\text{C}_{10}\text{H}_7\text{NOS}_2$ .

Calcd.: C; 54.27, H; 3.19, N; 6.33.

20 Found: C; 54.33, H; 3.31, N; 6.25.

NMR (200 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 7.51-7.64 (5H, m), 7.66 (1H, s).

IR (KBr)  $\text{cm}^{-1}$ : 3170, 3070, 2850, 1705, 1680, 1590, 1440, 680, 530.

##### ii) Synthesis of 4-[4-(5-benzylidenerhodanine)butylthio]pyridine

25 To a solution of 2.0 g (9.04 mmol) of 5-benzylidenerhodanine and 1.83 g (9.04 mmol) of 4-(4-chlorobutylthio)pyridine in 80 ml of dimethylformamide, 1.35 ml (9.04 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 2 : 1) to give 1.47 g of the desired compound (39.2% yield, pale yellow crystals).

30 NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.72-1.98 (4H, m), 3.04 (2H, t,  $J=7.2$  Hz), 4.18 (2H, t,  $J=6.8$  Hz), 7.11 (2H, dd,  $J=1.6, 4.6$  Hz), 7.45-7.58 (5H, m), 7.75 (1H, s), 8.39 (2H, dd,  $J=1.6, 4.6$  Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3020, 2940, 1710, 1580, 1340, 800, 760, 690.

### Example 154

#### Synthesis of 4-[3-(5-benzylidene-2,4-thiazolidinedione)propylthio]pyridine

40 To a solution of 2.0 g (9.74 mmol) of 5-benzylidene-2,4-thiazolidinedione and 1.83 g (9.74 mmol) of 4-(3-chloropropylthio)pyridine in 80 ml of dimethylformamide, 1.46 ml (9.74 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 2 : 1) to give 1.92 g of the desired compound (55.4% yield, pale yellow crystals).

45 NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.10 (2H, quint.,  $J=7.4$  Hz), 3.02 (2H, t,  $J=7.2$  Hz), 3.93 (2H, t,  $J=7.0$  Hz), 7.11 (2H, dd,  $J=1.8, 4.6$  Hz), 7.45-7.54 (5H, m), 7.91 (1H, s), 8.40 (2H, dd,  $J=1.4, 4.4$  Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3030, 2950, 1755, 1685, 1605, 1580, 1380, 800, 760, 710, 685.

### 50 Example 155

#### Synthesis of 4-[2-(5-benzylidene-2,4-thiazolidinedione)ethylthio]pyridine

55 To a solution of 2.0 g (9.74 mmol) of 5-benzylidene-2,4-thiazolidinedione and 1.69 g (9.74 mmol) of 4-(2-chloroethylthio)pyridine in 80 ml of dimethylformamide, 1.46 ml (9.74 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 2 : 1) to give

1.33 g of the desired compound (39.8% yield, pale yellow crystals).

Anal. for  $C_{17}H_{14}N_2O_2S_2$ .

Calcd.: C; 59.63, H; 4.12, N; 8.18.

Found: C; 59.54, H; 3.99, N; 8.04.

5 NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 3.27 (2H, t,  $J=7.8$  Hz), 4.05 (2H, t,  $J=7.4$  Hz), 7.27 (2H, dd,  $J=1.6, 4.2$  Hz), 7.46-7.54 (5H, m), 7.93 (1H, s), 8.46 (2H, dd,  $J=1.4, 4.4$  Hz).

IR (KBr)  $cm^{-1}$ : 3030, 1754, 1680, 1605, 1580, 800, 770, 710, 690.

#### Example 156

10

Synthesis of 4-[4-(isoindolin-1-on-2-yl)butyloxy]pyridine

The desired compound was synthesized in the same manner as described in Example 101.

15 NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.72-2.05 (4H, m), 3.60 (2H, t,  $J=6.6$  Hz), 4.09 (2H, t,  $J=6.2$  Hz), 5.34 (2H, s), 6.80 (2H, dd,  $J=4.8, 1.6$  Hz), 7.31-7.57 (3H, m), 7.85 (1H, d,  $J=6.6$  Hz), 8.40 (2H, dd,  $J=4.8, 1.6$  Hz).

IR (KBr)  $cm^{-1}$ : 1700, 1685, 1595, 1585, 1570, 1505.

#### Example 157

20 Synthesis of 4-[4-[5-(2-thienylmethylene)-2,4-thiazolidinedione]butylthio]pyridine

i) Synthesis of 5-(2-thienylmethylene)-2,4-thiazolidinedione

25 To a solution of 20 g (171 mmol) of 2,4-thiazolidinedione and 16.0 ml (171 mmol) of 2-thiophenecarboxaldehyde in 350 ml of ethanol, 1.68 ml (17.1 mmol) of piperidine was added, and the mixture was heated under reflux for 5 hours. After cooling, the precipitated crystals were filtered and washed with cooled ethanol to give 24.03 g of the desired compound (66.6% yield, pale yellow crystals).

Anal. for  $C_8H_5NO_2S_2$ .

Calcd.: C; 45.48, H; 2.39, N; 6.63.

30 Found: C; 45.41, H; 2.41, N; 6.52.

NMR (200 MHz,  $DMSO-d_6$ )  $\delta$ : 7.29 (1H, dd,  $J=3.6, 4.4$  Hz), 7.67 (1H, bd,  $J=3.6$  Hz), 8.01 (1H, bd,  $J=4.4$  Hz), 8.07 (1H, s).

IR (KBr)  $cm^{-1}$ : 3450, 3130, 3040, 2800, 1740, 1690, 1600, 1330, 640, 540.

35 ii) Synthesis of 4-[4-[5-(2-thienylmethylene)-2,4-thiazolidinedione]butylthio]pyridine

40 To a solution of 2.5 g (11.8 mmol) of 5-(2-thienylmethylene)-2,4-thiazolidinedione and 1.99 g (9.86 mmol) of 4-(4-chlorobutylthio)pyridine in 100 ml of dimethylformamide, 1.76 ml (11.8 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 2 : 1) to give 2.35 g of the desired compound (52.8% yield, pale yellow crystals).

45 NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.68-1.95 (4H, m), 3.02 (2H, t,  $J=7.0$  Hz), 3.79 (2H, t,  $J=7.0$  Hz), 7.10 (2H, dd,  $J=1.6, 4.6$  Hz), 7.20 (1H, dd,  $J=3.8, 5.0$  Hz), 7.41 (1H, bd,  $J=4.2$  Hz), 7.67 (1H, bd,  $J=5.0$  Hz), 8.06 (1H, s), 8.38 (2H, dd,  $J=1.6, 4.8$  Hz).

IR (KBr)  $cm^{-1}$ : 3040, 2950, 1740, 1680, 1600, 1580, 1350, 800, 740, 700.

#### Example 158

50 Synthesis of 4-[4-[5-(4-dimethylaminobenzylidene)rhodanine]butylthio]pyridine

55 To a solution of 3.0 g (11.35 mmol) of 5-(4-dimethylaminobenzylidene)rhodanine and 1.91 g (9.46 mmol) of 4-(4-chlorobutylthio)pyridine in 100 ml of dimethylformamide, 1.41 ml (9.46 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 2 : 1) to give 1.89 g of the desired compound (38.8% yield, pale yellow crystals).

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.71-2.01 (4H, m), 3.03 (2H, t,  $J=7.2$  Hz), 3.09 (6H, s), 4.17 (2H, t,  $J=7.0$  Hz),

6.73 (2H, d, J=9.0 Hz), 7.10 (2H, dd, J=1.8, 4.8 Hz), 7.40 (2H, d, J=9.0 Hz), 7.67 (1H, s), 8.38 (2H, dd, J=1.8, 4.8 Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3030, 2950, 1700, 1620, 1580, 820, 800.

### 5 Example 159

Synthesis of 4-(5-benzylidene-2,4-thiazolidinedione)methylthiopyridine

#### 10 i) Synthesis of 4-chloromethylthiopyridine

To a solution of 5.56 g (50.0 mmol) of 4-mercaptopyridine and 8.97 ml (60.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene in 50 ml of dimethylformaldehyde, 3.90 ml (60.0 mmol) of bromochloromethane was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 16 hours.

15 Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: chloroform) to give 2.34 g of the desired compound (27.2% yield, pale yellow crystals).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.05 (2H, s), 7.30 (2H, dd, J=1.8, 4.6 Hz), 8.51 (2H, dd, J=1.6, 4.6 Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3020, 2950, 1570, 1480, 1405, 800, 735, 700, 645.

#### 20 ii) Synthesis of 4-(5-benzylidene-2,4-thiazolidinedione)methylthiopyridine

To a solution of 0.308 g (1.50 mmol) of 5-benzylidene-2,4-thiazolidinedione and 0.127 g (0.80 mmol) of 4-chloromethylthiopyridine in 8 ml of dimethylformamide, 0.12 ml (0.80 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 1) to give 0.13 g of the desired compound (50.0% yield, pale yellow crystals).

Anal. for  $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2\text{S}_2 \cdot 0.4\text{H}_2\text{O}$ .

Calcd.: C; 57.26, H; 3.84, N; 8.35.

30 Found: C; 57.56, H; 3.53, N; 8.43.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.23 (2H, s), 7.41 (2H, bd, J=6.0 Hz), 7.46-7.52 (5H, m), 7.95 (1H, s), 8.49 (2H, bs).

IR (KBr)  $\text{cm}^{-1}$ : 3030, 2920, 1740, 1690, 1575, 1370, 810, 760, 685.

### 35 Example 160

Synthesis of 4-[4-(2,4-thiazolidinedione)butylthio]pyridine

40 To a solution of 2.34 g (20.0 mmol) of 2,4-thiazolidinedione and 4.03 g (20.0 mmol) of 4-(4-chlorobutylthio)pyridine in 120 ml of dimethylformamide, 3.0 ml (20 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 2 : 1 to ethyl acetate) to give 3.50 g of the desired compound (62.0% yield, pale yellow crystals).

45 Anal. for  $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2$ .

Calcd.: C; 51.04, H; 5.00, N; 9.92.

Found: C; 50.73, H; 4.92, N; 9.94.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.63-1.88 (4H, m), 3.00 (2H, t, J=7.0 Hz), 3.67 (2H, t, J=6.8 Hz), 3.95 (2H, s), 7.10 (2H, dd, J=1.6, 4.6 Hz), 8.40 (2H, dd, J=1.6, 4.6 Hz).

50 IR (KBr)  $\text{cm}^{-1}$ : 3040, 2950, 2930, 1750, 1685, 1580, 1380, 1355, 900, 800, 710.

### Example 161

Synthesis of 4-[4-(2-hydroxybenzoylamino)butylthio]pyridine

55 To a solution of 12.50 g (40 mmol) of 4-(phthalimidobutylthio)pyridine in 200 ml of ethanol, 5.82 ml (120 mmol) of hydrazine monohydrate was added, and the mixture was stirred at room temperature for 4 hours. Then, 200 ml of ethyl acetate was added, and the precipitated materials were filtered off. The solvent was distilled

off from the filtrate and chloroform was added to the residue. The mixture was washed with saturated saline and dried over anhydrous magnesium sulfate. The solvent was distilled off, and 400 ml of methylene chloride and 8.36 ml (60 mmol) of triethylamine were added to the residue. Then, 9.53 g (48 mmol) of O-acetylsalicyloyl chloride was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 1 hour. The mixture was washed with saturated saline and the solvent was distilled off from the mixture, after which 62.4 ml of ethanol and 62.4 ml of 1N-NaOH were added to the residue and the mixture was stirred for 15 minutes. Then, 62.4 ml of 1N-HCl was added, and ethanol was distilled off, after which the residue was extracted with chloroform and the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 5.48 g of the desired compound (45.3% yield, colorless solid), mp. 83-85°C.

Anal. for  $C_{16}H_{18}N_2O_2S$ .

Calcd.: C; 63.55, H; 6.00, N; 9.26.

Found: C; 63.27, H; 5.87, N; 8.96.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.72-1.93 (4H, m), 3.04 (2H, m), 3.51 (2H, m), 6.50 (1H, br), 6.83 (1H, m), 6.99 (1H, dd,  $J=8.4, 1.0$  Hz), 7.12 (2H, m), 7.29-7.44 (2H, m), 8.38 (2H, m).

IR (KBr)  $cm^{-1}$ : 3240, 1640, 1595, 1585, 1545, 1490.

#### Example 162

##### Synthesis of 3-[4-(4-pyridylthio)butyl]-2H-1,3-benzoxadine-2-thion-4(3H)-one

To a solution of 2.43 g (8.04 mmol) of 4-[4-(2-hydroxybenzoylamino) butylthio]pyridine in 80 ml of dry tetrahydrofuran, 2.86 g (16.05 mmol) of 1,1'-thiocarbonyl-diimidazole was added, and the mixture was stirred at room temperature for 70 hours. The solvent was distilled off and chloroform was added to the residue. The mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/n-hexane = 2 : 1) to give 2.28 g of the desired compound (82.3% yield, colorless crystals), mp. 93-94°C.

Anal. for  $C_{17}H_{16}N_2O_2S_2$ .

Calcd.: C; 59.28, H; 4.68, N; 8.13.

Found: C; 59.27, H; 4.72, N; 8.17.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.83 (2H, m), 2.01 (2H, m), 3.06 (2H, t,  $J=7.2$  Hz), 4.49 (2H, m), 7.11 (2H, m), 7.32-7.46 (2H, m), 7.75 (1H, m), 8.07 (1H, m), 8.39 (2H, m).

IR (KBr)  $cm^{-1}$ : 1715, 1620, 1600, 1575.

#### Example 163

##### Synthesis of 4-(4-rhodaninebutylthio)pyridine

To a solution of 4.0 g (30.0 mmol) of rhodanine and 6.05 g (30.0 mmol) of 4-(4-chlorobutylthio)pyridine in 150 ml of dimethylformamide, 4.49 ml (30.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 2 : 1 to ethyl acetate) to give 1.75 g of the desired compound (19.6% yield, pale brown crystals).

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.66-1.93 (4H, m), 3.01 (2H, t,  $J=7.0$  Hz), 3.97 (2H, s), 4.02 (2H, t,  $J=7.0$  Hz), 7.10 (2H, dd,  $J=1.6, 4.6$  Hz), 8.39 (2H, dd,  $J=1.6, 4.6$  Hz).

IR (KBr)  $cm^{-1}$ : 3040, 2950, 1730, 1710, 1580, 1360, 1280, 1225, 1140, 810, 715.

#### Example 164

##### Synthesis of 2-[4-(5-benzylidene-2,4-thiazolidinedione)butylthio]pyridine

###### i) Synthesis of 2-(4-chlorobutylthio)pyridine

To a solution of 25.0 g (225 mmol) of 2-mercaptopyridine and 34.5 ml (247 mmol) of triethylamine in 300 ml of ethanol, 28.5 ml (247 mmol) of 1-bromo-4-chlorobutane was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 16 hours. The solvent was distilled off and the residue was dissolved in chloroform. The solution was washed with saturated aqueous sodium bicarbonate and water, and



dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 3) to give 29.73 g of the desired compound (65.5% yield, pale yellow oil).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.70-2.05 (4H, m), 3.21 (2H, t,  $J=6.8$  Hz), 3.58 (2H, t,  $J=6.2$  Hz), 6.98 (1H, ddd,  $J=1.2, 5.0, 7.4$  Hz), 7.17 (1H, d,  $J=8.0$  Hz), 7.48 (1H, ddd,  $J=1.8, 7.2, 7.8$  Hz), 8.40-8.45 (1H, m).

## ii) Synthesis of 2-[4-(5-benzylidene-2,4-thiazolidinedione)butylthio]pyridine

To a solution of 4.10 g (20.0 mmol) of 5-benzylidene-2,4-thiazolidinedione and 4.03 g (20.0 mmol) of 2-(4-chlorobutylthio)pyridine in 80 ml of dimethylformamide, 3.0 ml (20.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 3) to give 3.89 g of the desired compound (52.5% yield, pale yellow crystals).

Anal. for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2\text{S}_2$ .

Calcd.: C; 61.60, H; 4.90, N; 7.56.

Found: C; 61.62, H; 4.86, N; 7.56.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.67-1.93 (4H, m), 3.21 (2H, t,  $J=6.8$  Hz), 3.79 (2H, t,  $J=7.0$  Hz), 6.95 (1H, ddd,  $J=1.0, 5.0, 7.4$  Hz), 7.15 (1H, ddd,  $J=1.0, 1.2, 8.2$  Hz), 7.41-7.51 (6H, m), 7.26 (1H, s), 8.41 (1H, m).

IR (KBr)  $\text{cm}^{-1}$ : 3060, 3040, 2950, 2930, 1675, 1605, 1580, 1365, 1130, 755, 690.

## Example 165

### Synthesis of 4-[5-(2-thienylmethylene)-2,4-thiazolidinedione)methylthio]pyridine

To a solution of 1.72 g (8.14 mmol) of 5-(2-thienylmethylene)-2,4-thiazolidinedione and 1.30 g (8.14 mmol) of 4-chloromethylthiopyridine in 80 ml of dimethylformamide, 1.22 ml (8.14 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 2 to 1 : 4) to give 1.88 g of the desired compound (69.0% yield, pale yellow crystals).

Anal. for  $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2\text{S}_3$ .

Calcd.: C; 50.28, H; 3.01, N; 8.38.

Found: C; 49.95, H; 3.00, N; 8.25.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.21 (2H, s), 7.20 (1H, dd,  $J=3.8, 5.0$  Hz), 7.39-7.43 (3H, m), 7.67-7.71 (1H, m), 8.10 (1H, s), 8.48 (2H, bd,  $J=5.4$  Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3040, 1740, 1680, 1600, 1580, 730.

## Example 166

### Synthesis of 4-(4-saccharinbutylthio)pyridine

To a solution of 2.75 g (15.0 mmol) of saccharin and 3.03 g (15.0 mmol) of 4-(4-chlorobutylthio)pyridine in 100 ml of dimethylformamide, 2.24 ml (15.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 2 to 4 : 1) to give 1.16 g of the desired compound (22.2% yield, white crystals).

Anal. for  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3\text{S}_2$ .

Calcd.: C; 55.15, H; 4.63, N; 8.04.

Found: C; 55.00, H; 4.33, N; 8.00.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.80-2.12 (4H, m), 3.04 (2H, t,  $J=7.2$  Hz), 3.83 (1H, t,  $J=7.0$  Hz), 7.10 (2H, dd,  $J=1.4, 4.6$  Hz), 7.79-7.96 (3H, m), 8.04-8.08 (1H, m), 8.37 (2H, bd,  $J=6.0$  Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3080, 2960, 1740, 1580, 1325, 1305, 1185, 760, 680.

Example 167

## Synthesis of 4-(4-(5,5-dimethyloxazolidine-2,4-dione)butylthio)pyridine

5 To a solution of 1.29 g (10.0 mmol) of 5,5-dimethyloxazolidine-2,4-dione and 2.02 g (10.0 mmol) 4-(4-chlorobutylthio)pyridine in 80 ml of dimethylformamide, 1.50 ml (10.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 1 → 2 : 1) to give  
 10 2.44 g of the desired compound (82.9% yield, colorless oil).

NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.55 (6H, s), 1.66-1.93 (4H, m), 3.02 (2H, t, J=7.0 Hz), 3.57 (2H, t, J=6.8 Hz), 7.09 (2H, dd, J=1.6, 4.6 Hz), 8.39 (2H, dd, J=1.6, 4.6 Hz).

IR (KBr) cm<sup>-1</sup>: 3040, 2950, 1820, 1740, 1580, 1450, 1420, 1100, 805, 780, 710.

Example 168

## Synthesis of 4-[2-(2-hydroxybenzoyl)aminoethylthio]pyridine

20 To a solution of 5.69 g (20.0 mmol) of 4-(2-phthalimidoethylthio)pyridine in 100 ml of ethanol, 2.91 ml (60.0 mmol) of hydrazine monohydrate was added, and the mixture was stirred at room temperature for 5 hours. The solvent was distilled off and the residue was dissolved in chloroform. The precipitate was filtered and the filtrate was concentrated. The resulting residue was used for the subsequent reaction.

To a solution of the above residue and 4.18 ml (30.0 mmol) of triethylamine in 100 ml of methylene chloride, 4.97 g (25.0 mmol) of O-acetylsalicyloyl chloride was added with stirring under ice-cooling, and the mixture  
 25 was stirred at room temperature for 2 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate and water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: methylene chloride/acetone = 8 : 1 to 2 : 1) to give 2.21 g of the desired compound (40.3% yield, white crystals).

30 NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.79 (1H, bs), 3.28 (2H, t, J=6.8 Hz), 1.56-1.67 (2H, m), 3.74 (2H, q, J=6.4 Hz), 6.84 (1H, ddd, J=1.2, 7.1, 7.2 Hz), 7.00 (2H, bd, J=7.8 Hz), 7.08 (1H, bs), 7.23 (2H, bd, J=6.2 Hz), 7.36-7.45 (2H, m), 8.42 (2H, bd, J=4.0 Hz).

IR (KBr) cm<sup>-1</sup>: 3440, 3250, 3080, 2930, 1640, 1595, 1580, 1495, 1340, 805, 760.

Example 169

## 35 Synthesis of 4-(2,4-thiazolidinedionemethylthio)pyridine

To a solution of 1.76 g (15.0 mmol) of 2,4-thiazolidinedione and 2.39 g (15.0 mmol) of 4-chloromethylthio-pyridine in 100 ml of dimethylformamide, 2.24 ml (15.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 2 : 1 to ethyl acetate) to give  
 40 1.49 g of the desired compound (41.5% yield, pale yellow crystals).

Anal. for C<sub>9</sub>H<sub>7</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>.

45 Calcd.: C; 44.98, H; 3.36, N; 11.66.

Found: C; 44.94, H; 3.41, N; 11.61.

NMR (200 MHz, CDCl<sub>3</sub>) δ: 3.99 (2H, s), 5.10 (2H, s), 7.37 (2H, dd, J=1.6, 4.6 Hz), 8.48 (2H, bd, J=6.0 Hz).

IR (KBr) cm<sup>-1</sup>: 3080, 3010, 2940, 1755, 1680, 1570, 895, 805.

50

Example 170

## Synthesis of 4-[2-[2H-1,3-benzoxadine-2-thion-4(3H)-on]ethylthio]pyridine

## 55 i) Synthesis of 4-[2-(2-hydroxybenzoyl)aminoethylthio]pyridine

To a solution of 3.50 g (12.3 mmol) of 4-(2-phthalimidoethylthio)pyridine in 80 ml of ethanol, 1.80 ml (37.0 mmol) of hydrazine monohydrate was added, and the mixture was stirred at room temperature for 5 hours. The

solvent was distilled off and the residue was dissolved in chloroform. The precipitate was filtered and the filtrate was concentrated. The resulting residue was used for the subsequent reaction.

To a solution of the above residue and 4.18 ml (30.0 mmol) of triethylamine in 100 ml of methylene chloride, 4.97 g (25.0 mmol) of O-acetylsalicyloyl chloride was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate and water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: methylene chloride/acetone = 8 : 1 to 2 : 1) to give 1.73 g of the desired compound (51.3% yield, white crystals).

#### 10 ii) Synthesis of 4-[2-[2H-1,3-benzoxadine-2-thion-4(3H)-on]ethylthio]pyridine

To a solution of 4-[2-(2-hydroxybenzoyl)aminoethylthio]pyridine in 70 ml of tetrahydrofuran, 1.13 g (6.31 mmol) of 1,1'-thiocarbonyldiimidazole was added under nitrogen atmosphere, and the mixture was stirred at room temperature for 64 hours. The solvent was distilled off and the residue was dissolved in chloroform. The solution was washed with water and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 1.40 g of the desired compound (70.0% yield, white crystals).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.41 (2H, dd,  $J=7.8, 8.0$  Hz), 4.74 (2H, dd,  $J=7.8, 8.0$  Hz), 7.34-7.49 (4H, m), 7.77 (1H, ddd,  $J=1.8, 7.4, 9.0$  Hz), 8.10 (1H, dd,  $J=1.8, 8.0$  Hz), 8.45 (2H, bs).

IR (KBr)  $\text{cm}^{-1}$ : 3020, 2350, 1705, 1620, 1475, 1320, 800, 755, 700.

#### 20 Example 171

##### Synthesis of 4-[4-(5-propylmethylene-2,4-thiazolidinedione)butylthio]pyridine

To a solution of 0.5 g (1.77 mmol) of 4-[4-(2,4-thiazolidinedione)butylthio]pyridine and 0.16 ml (1.77 mmol) of butylaldehyde in 25 ml of ethanol, 0.02 ml (0.18 mmol) of piperidine was added, and the mixture was heated under reflux for 2 hours. After cooling, the solvent was distilled off and the residue was dissolved in ethyl acetate. The solution was washed with water and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: hexane/ethyl acetate = 2 : 1 to 1 : 1) to give 0.42 g of the desired compound (70.6% yield, yellow oil).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.98 (3H, t,  $J=7.2$  Hz), 1.50-1.68 (2H, m), 1.69-1.88 (4H, m), 2.22 (2H, q,  $J=7.4$  Hz), 3.01 (2H, t,  $J=7.0$  Hz), 3.73 (2H, t,  $J=6.8$  Hz), 7.08 (1H, t,  $J=7.8$  Hz), 7.09 (2H, dd,  $J=1.8, 4.6$  Hz), 8.38 (2H, dd,  $J=1.6, 4.6$  Hz).

IR (neat)  $\text{cm}^{-1}$ : 3030, 2955, 2930, 1740, 1680, 1580, 1480, 800, 705.

#### 35 Example 172

##### Synthesis of 4-saccharinmethylthiopyridine

To a solution of 2.75 g (15.0 mmol) of saccharin and 3.03 g (15.0 mmol) of 4-chloromethylthiopyridine in 100 ml of dimethylformamide, 2.24 ml (15.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 2 to 4 : 1) to give 1.73 g of the desired compound (37.7% yield, pale yellow crystals).

Anal. for  $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_3\text{S}_2$ .

Calcd.: C; 50.97, H; 3.29, N; 9.14.

Found: C; 50.66, H; 3.27, N; 9.11.

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.32 (2H, s), 7.42 (2H, dd,  $J=1.6, 4.6$  Hz), 7.81-7.96 (3H, m), 8.08-8.11 (1H, m), 8.50 (2H, dd,  $J=1.6, 4.6$  Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3090, 3030, 1740, 1570, 1400, 1340, 1180, 800, 750, 670.

#### Example 173

##### 55 Synthesis of 4-(5,5-dimethyloxazolidine-2,4-dione)methylthiopyridine

To a solution of 1.93 g (15.0 mmol) of 5,5-dimethyloxazolidine-2,4-dione and 2.40 g (15.0 mmol) of 4-chloromethylthiopyridine in 100 ml of dimethylformamide, 2.24 ml (15.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-unde-

cene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 2 to 2 : 1) to give 2.32 g of the desired compound (61.3% yield, yellow crystals).

Anal. for  $C_{11}H_{12}N_2O_3S$ .

Calcd.: C; 52.37, H; 4.79, N; 11.10.

Found: C; 52.08, H; 4.94, N; 11.06.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.54 (6H, s), 5.01 (2H, s), 7.38 (2H, dd,  $J=1.6, 4.6$  Hz), 8.49 (2H, dd,  $J=1.6, 4.6$  Hz).

IR (KBr)  $cm^{-1}$ : 3030, 2980, 1810, 1740, 1580, 800, 770, 700.

#### Example 174

##### Synthesis of 4-[3-(2-quinoxaloylamino)propylthio]pyridine

To a solution of 4.30 g (17.8 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride and 8.68 ml (62.3 mmol) of triethylamine in 200 ml of methylene chloride, 3.43 g (17.8 mmol) of 2-quinoxaloyl chloride was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate and water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) and recrystallization (solvent: ethyl acetate-ether) to give 2.82 g of the desired compound (48.9% yield, white crystals).

Anal. for  $C_{17}H_{16}N_4OS$ .

Calcd.: C; 62.94, H; 4.97, N; 17.27.

Found: C; 62.97, H; 5.06, N; 17.25.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 2.14 (2H, quint.,  $J=7.0$  Hz), 3.13 (2H, t,  $J=7.4$  Hz), 3.73 (2H, q,  $J=6.7$  Hz), 7.14 (2H, dd,  $J=1.4, 4.6$  Hz), 7.82-7.94 (2H, m), 8.09-8.24 (3H, m), 8.40 (2H, dd,  $J=1.4, 4.6$  Hz), 9.69 (1H, s).  
IR (KBr)  $cm^{-1}$ : 1680, 1580, 800, 760.

#### Example 175

30

##### Synthesis of 4-[4-[5-(3,5-di-tert-butyl-4-hydroxyphenyl)methylene-2,4-thiazolidinedione]butylthio]pyridine

###### i) Synthesis of 5-(3,5-di-tert-butyl-4-hydroxyphenyl)methylene-2,4-thiazolidinedione

To a solution of 12.5 g (107 mmol) of 2,4-thiazolidinedione and 25.0 g (107 mmol) of 3,5-di-tert-butyl-4-hydroxybenzaldehyde in 300 ml of ethanol, 1.05 ml (10.7 mmol) of piperidine was added, and the mixture was heated under reflux for 5 hours. After cooling, the precipitated crystals were filtered and washed with cooled ethanol to give 15.23 g of the desired compound (42.8% yield, pale yellow crystals).

NMR (200 MHz,  $DMSO-d_6$ )  $\delta$ : 1.41 (18H, s), 7.37 (2H, s), 7.76 (2H, s), 12.44 (1H, bs).

IR (KBr)  $cm^{-1}$ : 3620, 3440, 2960, 1740, 1690, 700, 650.

###### ii) Synthesis of 4-[4-[5-(3,5-di-tert-butyl-4-hydroxyphenyl)methylene-2,4-thiazolidinedione]butylthio]pyridine

To a solution of 5.0 g (15.0 mmol) of 5-(3,5-di-tert-butyl-4-hydroxyphenyl)methylene-2,4-thiazolidinedione and 3.02 g (15.0 mmol) of 4-(4-chlorobutylthio)pyridine in 100 ml of dimethylformamide, 2.24 ml (15.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 2 : 1) and recrystallization (solvent: ethyl acetate-ether) to give 3.83 g of the desired compound (51.3% yield, pale yellow crystals).

Anal. for  $C_{27}H_{34}N_2O_3S_2$ .

Calcd.: C; 65.03, H; 6.87, N; 5.62.

Found: C; 64.92, H; 6.78, N; 5.48.

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.47 (18H, s), 1.67-1.95 (4H, m), 3.03 (2H, t,  $J=7.0$  Hz), 3.80 (2H, t,  $J=7.0$  Hz), 5.73 (1H, s), 7.11 (2H, dd,  $J=1.8, 4.8$  Hz), 7.37 (2H, s), 7.87 (1H, s), 8.39 (2H, dd,  $J=1.8, 4.8$  Hz).

IR (KBr)  $cm^{-1}$ : 2950, 1740, 1680, 1580, 1130, 800, 740.

Example 176

## Synthesis of 4-(2,4-thiazolidinedionemethylthio)pyridine hydrochloride

- 5 To a solution of 702.9 mg (2.92 mmol) of 4-(2,4-thiazolidinedionemethylthio)pyridine in 30 ml of methanol, 70 ml of 10% hydrochloric acid-methanol was added, and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off and the residue was purified by recrystallization (solvent: ethanol-ether) to give 689.9 mg of the desired compound (84.9% yield, pale yellow crystals).

Anal. for  $C_9H_8N_2O_2S_2 \cdot HCl$ ,

10 Calcd.: C; 39.06, H; 3.28, N; 10.12.

Found: C; 38.85, H; 2.99, N; 10.10.

NMR (200 MHz,  $D_2O$ , ref=4.80 ppm of HDO)  $\delta$ : 4.18 (2H, s), 5.38 (2H, s), 8.05 (2H, bd, J=7.2 Hz), 8.50 (2H, bd, J=7.2 Hz).

IR (KBr)  $cm^{-1}$ : 1670, 1625, 1370, 1140, 800.

15

Example 177

## Synthesis of 4-[4-[5-(3,5-di-tert-butyl-4-hydroxyphenyl)methylenerrhodanine]butylthio]pyridine

- 20 i) Synthesis of 5-(3,5-di-tert-butyl-4-hydroxyphenyl)methylenerrhodanine

To a solution of 14.6 g (110 mmol) of rhodanine and 25.7 g (110 mmol) of 3,5-di-tert-butyl-4-hydroxybenzaldehyde in 150 ml of ethanol, 1.08 ml (11.0 mmol) of piperidine was added, and the mixture was treated under reflux for 5 hours. After cooling, the precipitated crystals were filtered and washed with cooled ethanol to give 25 26.71 g of the desired compound (69.7% yield, pale yellow crystals).

Anal. for  $C_{18}H_{23}NO_2S_2$ ,

Calcd.: C; 61.86, H; 6.63, N; 4.01.

Found: C; 61.95, H; 6.50, N; 3.96.

NMR (200 MHz,  $DMSO-d_6$ )  $\delta$ : 1.42 (18H, s), 7.37 (2H, s), 7.69 (1H, s), 7.76 (1H, s), 12.44 (1H, s).

30 IR (KBr)  $cm^{-1}$ : 3620, 2960, 1700, 1580, 1420, 1180, 690, 660.

- ii) Synthesis of 4-[4-[5-(3,5-di-tert-butyl-4-hydroxyphenyl)methylenerrhodanine]butylthio]pyridine

To a solution of 5.24 g (15.0 mmol) of 5-(3,5-di-tert-butyl-4-hydroxyphenyl)methylenerrhodanine and 3.02 35 g (15.0 mmol) of 4-(4-chlorobutylthio)pyridine in 100 ml of dimethylformamide, 2.24 ml (15.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/hexane = 1 : 1) and recrystallization (solvent: ethyl acetate-ether) to give 2.21 g of the desired compound (28.6% yield, 40 pale yellow crystals).

Anal. for  $C_{27}H_{34}N_2O_2S_3$ ,

Calcd.: C; 63.00, H; 6.66, N; 5.44.

Found: C; 62.89, H; 6.79, N; 5.35.

45 NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.48 (18H, s), 1.71-2.03 (4H, m), 3.04 (2H, t, J=7.0 Hz), 4.18 (2H, t, J=7.0 Hz), 5.79 (1H, s), 7.11 (2H, bd, J=6.4 Hz), 7.36 (2H, s), 7.72 (1H, s), 8.40 (2H, bd, J=6.4 Hz).

IR (KBr)  $cm^{-1}$ : 2950, 1705, 1580, 1160, 800.

Example 178

- 50 Synthesis of 4-[3-(2-pyrazinecarbonylamino)propylthio]pyridine dihydrochloride

To a solution of 704.5 mg (2.57 mmol) of 4-[3-(2-pyrazinecarbonylamino)propylthio]pyridine in 30 ml of methanol, 70 ml of 10% hydrochloric acid-methanol was added, and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off and the residue was purified by recrystallization (solvent: ethanol- 55 ether) to give 842.4 mg of the desired compound (85.6% yield, pale yellow crystals).

Anal. for  $C_{13}H_{14}N_4OS \cdot 2HCl$ ,

Calcd.: C; 44.96, H; 4.64, N; 16.13, S; 9.23, Cl; 20.42.

Found: C; 44.96, H; 4.55, N; 16.00, S; 9.23, Cl; 20.19.

NMR (200 MHz, D<sub>2</sub>O, ref=4.80 ppm of HDO)  $\delta$ : 2.09 (2H, quint., J=6.6 Hz), 3.27 (2H, t, J=7.4 Hz), 3.59 (2H, t, J=6.6 Hz), 7.73 (2H, bd, J=6.8 Hz), 8.72 (2H, bd, J=7.6 Hz), 9.08 (1H, s).  
 IR (KBr) cm<sup>-1</sup>: 3450, 3230, 3050, 1680, 1620, 1480, 800, 620.

#### 5     Example 179

Synthesis of 4-(5,5-dimethyloxazolidine-2,4-dionemethylthio)pyridine hydrochloride

To a solution of 627.2 mg (2.49 mmol) of 4-(5,5-dimethyloxazolidine-2,4-dionemethylthio)pyridine in 30 ml of methanol, 70 ml of 10% hydrochloric acid-methanol was added, and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off and the residue was purified by recrystallization (solvent: ethanol-ether) to give 631.5 mg of the desired compound (88.0% yield, white crystals).

Anal. for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S·HCl.

Calcd.: C; 45.76, H; 4.54, N; 9.70.

15     Found: C; 45.62, H; 4.60, N; 9.66.

NMR (200 MHz, D<sub>2</sub>O, ref=4.80 ppm of HDO)  $\delta$ : 1.57 (6H, s), 5.38 (2H, s), 8.07 (2H, d, J=7.2 Hz), 8.54 (2H, d, J=7.2 Hz).

IR (KBr) cm<sup>-1</sup>: 1745, 1620, 1595, 1480, 815, 780.

#### 20     Example 180

Synthesis of 4-(saccharinmethylthio)pyridine hydrochloride

To a solution of 589.9 mg (1.93 mmol) of 4-(saccharinmethylthio)pyridine in 30 ml of methanol, 70 ml of 10% hydrochloric acid-methanol was added, and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off and the residue was purified by recrystallization (solvent: ethanol-ether) to give 607.6 mg of the desired compound (91.7% yield, pale yellow crystals).

Anal. for C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>S·HCl.

Calcd.: C; 45.55, H; 3.23, N; 8.17.

30     Found: C; 45.45, H; 3.33, N; 8.17.

NMR (200 MHz, D<sub>2</sub>O, ref=4.80 ppm of HDO)  $\delta$ : 5.67 (2H, s), 7.90-8.07 (6H, m), 8.55 (2H, bd, J=7.0 Hz).

IR (KBr) cm<sup>-1</sup>: 3040, 2980, 1735, 1630, 1595, 1355, 1285, 1250, 1180, 800, 760.

#### Example 181

35

Synthesis of 3-[3-(2-pyridylthio)propyl]-2H-1,3-benzoxadine-2-thion-4(3H)-one

To a solution of 1.153 g (4.00 mmol) of 2-[3-(2-hydroxybenzoylamino)propylthio]pyridine in 60 ml of dry tetrahydrofuran, 1.426 g (8.00 mmol) of 1,1'-thiocarbonyl-diimidazole was added, and the mixture was stirred at room temperature for 64 hours. The solvent was distilled off and chloroform was added to the residue. The mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/n-hexane = 1 : 4) to give 0.72 g of the desired compound (54.5% yield, colorless crystals), mp. 83-84°C.

Anal. for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>.

45     Calcd.: C; 58.16, H; 4.27, N; 8.48.

Found: C; 58.05, H; 4.21, N; 8.33.

NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.25 (2H, m), 3.30 (2H, t, J=7.2 Hz), 4.62 (2H, m), 6.97 (1H, m), 7.19 (1H, d, J=8 Hz), 7.32-7.53 (3H, m), 7.74 (1H, m), 8.08 (1H, m), 8.38 (1H, m).

#### 50     Example 182

Synthesis of 3-[3-(2-pyridylthio)propyl]-2H-1,3-benzoxadine-2,4(3H)-dione

To a solution of 1.153 g (4.0 mmol) of 2-[3-(2-hydroxybenzoylamino)propylthio]pyridine in 60 ml of dry tetrahydrofuran, 1.30 g (10.0 mmol) of 1,1'-carbonyldiimidazole was added, and the mixture was stirred at room temperature for 16 hours. The solvent was distilled off and chloroform was added to the residue. The mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/n-hexane = 1 : 3) to give 1.07 g of the de-

sired compound (85.1% yield, colorless viscous liquid).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.16 (2H, m), 3.26 (2H, t,  $J=7.2$  Hz), 4.21 (2H, t,  $J=7$  Hz), 6.95 (1H, m), 7.16 (1H, m), 7.24-7.50 (3H, m), 7.71 (1H, m), 8.09 (1H, dd,  $J=8$ , 1.6 Hz), 8.34 (1H, m).

IR (neat)  $\text{cm}^{-1}$ : 1760, 1700, 1685, 1620, 1585.

#### Example 183

Synthesis of 4-[4-[5-(3-thienyl)methylene-2,4-thiazolidinedione]butylthio]pyridine

To a solution of 1.41 g (5.0 mmol) of 4-[4-(2,4-thiazolidinedione)butylthio]pyridine and 0.44 ml (5.0 mmol) of 3-thiophenecarbaldehyde in 50 ml of ethanol, 0.05 ml (0.5 mmol) of piperidine was added, and the mixture was heated under reflux for 8 hours. After cooling, the solvent was distilled off. The residue was dissolved in chloroform, and the solution was washed with saturated aqueous sodium bicarbonate, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 1.43 g of the desired compound (76.0% yield, pale yellow crystals).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.68-1.94 (4H, m), 3.03 (2H, t,  $J=7.0$  Hz), 3.79 (2H, t,  $J=6.8$  Hz), 7.11 (2H, d,  $J=5.8$  Hz), 7.29 (1H, dd,  $J=1.2$ , 5.2 Hz), 7.45 (1H, dd,  $J=3.0$ , 5.2 Hz), 7.63 (1H, dd,  $J=1.4$ , 3.0 Hz), 7.90 (1H, s), 8.39 (2H, s).

IR (KBr)  $\text{cm}^{-1}$ : 3100, 2950, 1730, 1680, 1610, 1360, 1120, 780, 710, 620, 545.

#### Example 184

Synthesis of 4-[4-[5-(4-pyridyl)methylene-2,4-thiazolidinedione]butylthio]pyridine

To a solution of 1.41 g (5.0 mmol) of 4-[4-(2,4-thiazolidinedione)butylthio]pyridine and 0.48 ml (5.0 mmol) of 4-pyridinecarbaldehyde in 50 ml of ethanol, 0.05 ml (0.5 mmol) of piperidine was added, and the mixture was heated under reflux for 16 hours. After cooling, the solvent was distilled off. The residue was dissolved in chloroform, and the solution was washed with water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate to ethyl acetate/ethanol = 20 : 1 to 10 : 1) to give 0.666 g of the desired compound (35.9% yield, pale yellow crystals).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.68-1.98 (4H, m), 3.03 (2H, t,  $J=7.0$  Hz), 3.82 (2H, t,  $J=6.7$  Hz), 7.11 (2H, d,  $J=5.3$  Hz), 7.35 (2H, d,  $J=6.0$  Hz), 7.79 (1H, s), 8.39 (2H, s), 8.75 (2H, d,  $J=4.5$  Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3030, 2950, 1745, 1680, 1575, 1350, 1130, 805, 710, 650, 540.

#### Example 185

Synthesis of 4-[4-[5-(3-pyridyl)methylene-2,4-thiazolidinedione]butylthio]pyridine

To a solution of 1.41 g (5.0 mmol) of 4-[4-(2,4-thiazolidinedione)butylthio]pyridine and 0.47 ml (5.0 mmol) of 3-pyridylcarboxaldehyde in 50 ml of ethanol, 0.05 ml (0.5 mmol) of piperidine was added, and the mixture was heated under reflux for 16 hours. After cooling, the solvent was distilled off. The residue was dissolved in chloroform, and the solution was washed with water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 0.932 g of the desired compound (50.2% yield, pale yellow crystals).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.70-1.98 (4H, m), 3.04 (2H, t,  $J=7.0$  Hz), 3.82 (2H, t,  $J=6.8$  Hz), 7.12 (2H, dd,  $J=1.6$ , 4.6 Hz), 7.44 (1H, dd,  $J=4.6$ , 8.0 Hz), 7.81 (1H, ddd,  $J=1.8$ , 2.0, 8.0 Hz), 7.88 (1H, s), 8.40 (2H, d,  $J=4.8$  Hz), 8.66 (1H, dd,  $J=1.6$ , 4.8 Hz), 8.79 (1H, d,  $J=2.2$  Hz).

IR (KBr)  $\text{cm}^{-1}$ : 3030, 2840, 1740, 1675, 1610, 1365, 1130, 800, 705.

#### Example 186

Synthesis of 4-[4-[5-(2-pyridyl)methylene-2,4-thiazolidinedione]butylthio]pyridine

To a solution of 1.41 g (5.0 mmol) of 4-[4-(2,4-thiazolidinedione)butylthio]pyridine and 0.48 ml (5.0 mmol) of 2-pyridinecarbaldehyde in 50 ml of ethanol, 0.05 ml (0.5 mmol) of piperidine was added, and the mixture was heated under reflux for 16 hours. After cooling, the solvent was distilled off. The residue was dissolved in chloroform, and the solution was washed with water, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: hexane/ethyl acetate = 1 : 1 to ethyl acetate) to give 1.49 g

of the desired compound (80.2% yield, pale yellow crystals).

NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.67-1.94 (4H, m), 3.02 (2H, t, J=7.0 Hz), 3.80 (2H, t, J=6.6 Hz), 7.10 (2H, dd, J=1.4, 4.8 Hz), 7.28 (1H, ddd, J=1.0, 4.8, 7.8 Hz), 7.51 (1H, d, J=7.8 Hz), 7.78 (1H, ddd, J=1.8, 7.6, 7.8 Hz), 7.79 (1H, s), 8.38 (2H, d, J=4.8 Hz), 8.75 (1H, d, J=4.6 Hz).

IR (KBr) cm<sup>-1</sup>: 3040, 2950, 1730, 1670, 1575, 1390, 1130, 800, 710, 540.

#### Example 187

Synthesis of 4-[4-(5-nonylmethylene-2,4-thiazolidinedione)butylthio]pyridine hydrochloride

i) Synthesis of 4-[4-(5-nonylmethylene-2,4-thiazolidinedione)butylthio]pyridine

To a solution of 1.41 g (5.0 mmol) of 4-[4-(2,4-thiazolidinedione)butylthio]pyridine and 0.94 ml (5.0 mmol) of 1-decanal in 50 ml of ethanol, 0.05 ml (0.5 mmol) of piperidine was added, and the mixture was heated under reflux for 2 hours. After cooling, the solvent was distilled off. The residue was dissolved in ethyl acetate, and the solution was washed with saturated aqueous sodium bicarbonate, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: hexane/ethyl acetate = 5 : 1 to 1 : 1) to give 1.97 g of the desired compound (93.7% yield, yellow oil).

NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.88 (3H, t, J=7.2 Hz), 1.22-1.30 (12H, m), 1.46-1.60 (2H, m), 1.68-1.88 (4H, m), 2.23 (2H, q, J=7.6 Hz), 3.02 (2H, t, J=7.0 Hz), 3.74 (2H, t, J=6.8 Hz), 7.09 (1H, t, J=7.8 Hz), 7.12 (2H, d, J=4.6 Hz), 8.40 (2H, s).

IR (neat) cm<sup>-1</sup>: 3030, 2925, 2850, 1740, 1690, 1580, 1480, 1350, 800, 735, 710.

ii) Synthesis of 4-[4-(5-nonylmethylene-2,4-thiazolidinedione)butylthio]pyridine hydrochloride

To a solution of 1.83 g (4.35 mmol) of the above free amine in 40 ml of methanol, 200 ml of 10% hydrochloric acid/methanol was added, and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off and the residue was washed with ether to give 1.50 g of the desired product (75.4% yield, white solid).

NMR (200 MHz, D<sub>2</sub>O)  $\delta$ : 0.93 (3H, m), 1.32 (12H, m), 1.55 (2H, m), 1.77 (4H, m), 2.21 (2H, m), 3.21 (2H, m), 3.74 (2H, m), 7.04 (1H, t, J=7.4 Hz), 7.68 (2H, d, J=6.6 Hz), 8.45 (2H, d, J=6.0 Hz).

#### Example 188

Synthesis of 2-[4-[5-(2-thienyl)methylene-2,4-thiazolidinedione]butylthio]pyridine

To a solution of 2.11 g (10.0 mmol) of 5-(2-thienyl)methylene-2,4-thiazolidinedione and 2.02 g (10.0 mmol) of 2-(4-chlorobutylthio)pyridine in 100 ml of dimethylformamide, 1.50 ml (10.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: hexane/ethyl acetate = 3 : 1 to 2 : 1) to give 1.40 g of the desired compound (37.3% yield, pale yellow crystals).

NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.68-1.94 (4H, m), 3.22 (2H, t, J=7.0 Hz), 3.79 (2H, t, J=6.8 Hz), 6.97 (1H, ddd, J=1.0, 4.8, 7.2 Hz), 7.14-7.22 (2H, m), 7.41 (1H, d, J=3.8 Hz), 7.47 (1H, ddd, J=1.6, 8.0, 8.0 Hz), 7.66 (1H, d, J=5.2 Hz), 8.06 (1H, s), 8.42 (1H, dd, J=1.4, 4.0 Hz).

IR (KBr) cm<sup>-1</sup>: 1730, 1665, 1600, 1350, 1130, 755.

#### Example 189

Synthesis of 3-[4-[5-(2-thienyl)methylene-2,4-thiazolidinedione]butylthio]pyridine

i) 3-(4-chlorobutylthio)pyridine

To a solution of 2.73 g (15 mmol) of 3-(N,N-dimethylaminocarbonylthio)pyridine in 30 ml of methanol, 16.5 ml (33 mmol) of 2 N aqueous sodium hydroxide was added, and the mixture was heated under reflux for 30 minutes. After cooling, the pH of the reaction mixture was adjusted to about 5 with 1 N hydrochloric acid, and the solvent was distilled off.

To a solution of this crude product (3-mercaptopyridine) and 4.18 ml (30 mmol) of triethylamine in 30 ml of ethanol, 3.46 ml (30 mmol) of 4-bromo-1-chlorobutane was added, and the mixture was stirred at room tem-



perature for 4 hours. The solvent was distilled off and the residue was dissolved in methylene chloride. The solution was washed with saturated aqueous sodium bicarbonate, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: hexane/ethyl acetate = 5 : 1 to 1 : 1) to give 2.09 g of the desired compound (69.1% yield, yellow oil).

5 NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.74-2.01 (4H, m), 2.97 (2H, t,  $J=7.0$  Hz), 3.56 (2H, t,  $J=6.2$  Hz), 7.25 (1H, dd,  $J=4.8, 8.0$  Hz), 7.68 (1H, ddd,  $J=1.4, 1.8, 8.0$  Hz), 8.44 (1H, dd,  $J=1.4, 4.8$  Hz), 8.59 (1H, d,  $J=1.8$  Hz).

IR (neat)  $\text{cm}^{-1}$ : 3035, 2955, 2865, 1560, 1465, 1405, 1110, 1020, 795, 705, 650, 620.

10 ii) 3-[4-[5-(2-thienyl)methylene-2,4-thiazolidinedione]butylthio]pyridine

To a solution of 2.11 g (10.0 mmol) of 5-(2-thienyl)methylene-2,4-thiazolidinedione and 2.02 g (10.0 mmol) of 3-(4-chlorobutylthio)pyridine in 100 ml of dimethylformamide, 1.50 ml (10.0 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by recrystallization (solvent: chloroform/ethyl acetate/diethyl ether) to give 2.18 g of the product (57.9% yield, pale brown crystals).

15 NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.62-1.94 (4H, m), 2.97 (2H, t,  $J=7.0$  Hz), 3.69 (2H, t,  $J=7.0$  Hz), 7.18-7.22 (2H, m), 7.42 (1H, d,  $J=3.8$  Hz), 7.63-7.69 (2H, m), 8.07 (1H, s), 8.43 (1H, s), 8.59 (1H, s).

IR (KBr)  $\text{cm}^{-1}$ : 1740, 1670, 1600, 1350, 1120, 720.

20

Example 190

Synthesis of 4-[4-(5-isopropylidene-2,4-thiazolidinedione)butylthio]pyridine

25 i) 5-isopropylidene-2,4-thiazolidinedione

In a 300-ml flask equipped with an apparatus for dehydration, 10.0 g (90 mmol) of 2,4-thiazolidinedione and 15 ml (225 mmol) of acetone was placed, and 100 ml of benzene was added thereto. To this suspension, 0.5 ml (5 mmol) of piperidine and 0.25 ml (4 mmol) of glacial acetic acid were successively added, and the mixture was heated under reflux for 22 hours. After cooling, the solvent was distilled off. Although the residue was recrystallized from ethanol/chloroform/ether, it was not possible to separate the product from the starting material (2,4-thiazolidinedione). In the subsequent reaction, this mixture (starting material : desired product = 1 : 1.14, 4.55 g) was used without further purification.

30 NMR (200 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 1.94 (3H, s), 2.34 (3H, s), 12.06 (1H, s).

35

ii) 4-[4-(5-isopropylidene-2,4-thiazolidinedione)butylthio]pyridine

To a solution of 2.60 g (18.8 mmol) of the above mixture and 3.79 g (18.8 mmol) of 4-(4-chlorobutylthio)pyridine in 100 ml of dimethylformamide, 2.81 ml (18.8 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: hexane/ethyl acetate = 2 : 1 to 1 : 1 to 1 : 2 to ethyl acetate) to give 1.98 g of the desired product (61.4% yield, pale yellow powder).

40 NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.68-1.86 (4H, m), 2.00 (3H, s), 2.45 (3H, s), 3.01 (2H, t,  $J=7.0$  Hz), 3.71 (2H, t,  $J=6.8$  Hz), 7.11 (2H, d,  $J=6.2$  Hz), 8.38 (2H, s).

45

Example 191

Synthesis of 4-[(isoindolin-1-on-2-yl)methylthio]pyridine

50

To a solution of 681 mg (2.5 mmol) of 4-[(3-hydroxyisoindolin-1-on-2-yl)methylthio]pyridine in 6 ml of trifluoroacetic acid, 0.30 g (7.93 mmol) of sodium borohydride was added in small portions, and the mixture was stirred for 15 minutes. The reaction mixture was poured into cold water and aqueous ammonia was added to make the mixture basic, followed by extraction with methylene chloride. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified by recrystallization (solvent: ethyl acetate) to give 350 mg of the desired product (54.6% yield, colorless columns), mp. 131-132°C.

55

Anal. for  $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ ,

Calcd.: C; 65.60, H; 4.72, N; 10.93.

Found: C; 65.31, H; 4.64, N; 10.71.

#### Example 192

##### 5 Synthesis of 3-[4-(4-pyridylthio)butyl]quinazoline-2(1H)-thion-4(3H)-one

In a solution of 1.50 g (4.0 mmol) of 4-[4-(2-aminobenzoylamino)butylthio]pyridine dihydrochloride in 10 ml of methanol, 4.2 ml (8.4 mmol) of 2 N aqueous sodium hydroxide was added, and the mixture was stirred at room temperature for 1 hour. Wafer was added to the reaction mixture, and the mixture was extracted with  
10 chloroform. The extract was dried and the solvent was distilled off. The resulting free amine was used in the subsequent reaction without further purification.

Under nitrogen atmosphere, to a solution of the above free amine in 20 ml of tetrahydrofuran, 1.43 g (8.0 mmol) of 1,1'-thiocarbonyldiimidazole was added, and the mixture was stirred at room temperature for 16 hours. The solvent was distilled off and the residue was dissolved in chloroform. The solution was washed with water  
15 and dried. The solvent was distilled off and the residue was washed with chloroform/ethyl acetate to give 614 mg (44.8% yield, pale brown powder).

NMR (200 MHz, DMSO- $d_6$ )  $\delta$ : 1.64-1.94 (4H, m), 3.12 (2H, t, J=6.8 Hz), 4.44 (2H, t, J=7.4 Hz), 7.25 (2H, dd, J=1.4, 4.6 Hz), 7.29-7.41 (2H, m), 7.74 (1H, dt, J=1.4, 8.2 Hz), 7.96 (1H, dd, J=1.2, 8.0 Hz), 8.34 (2H, dd, J=1.4, 4.6 Hz).

20 IR (KBr)  $cm^{-1}$ : 1675, 1590, 1405, 1160, 760, 720.

#### Example 193

##### 25 Synthesis of 3-[3-(4-pyridylthio)propyl]quinazoline-2,4(1H,3H)-dione

Under nitrogen atmosphere, to a solution of 718 mg (2.5 mmol) of 4-[3-(2-aminobenzoylamino)propylthio]pyridine in 15 ml of tetrahydrofuran, 811 mg (5.0 mmol) of 1,1'-carbonyldiimidazole was added, and the mixture was stirred at room temperature for 16 hours. The solvent was distilled off and the residue was dissolved in chloroform. The solution was washed with water and dried. The solvent was distilled off and the residue was  
30 recrystallized from ethanol/chloroform/ether to give 514 mg of the desired product (65.7% yield, white crystals).

NMR (200 MHz, DMSO- $d_6$ )  $\delta$ : 1.97 (2H, quint., J=7.2 Hz), 3.12 (2H, t, J=7.4 Hz), 4.05 (2H, t, J=7.0 Hz), 7.16 7.27 (4H, m), 7.65 (1H, dt, J=1.4, 6.6 Hz), 8.35 (2H, d, J=6.0 Hz), 11.43 (1H, s).

IR (KBr)  $cm^{-1}$ : 1710, 1660, 1585, 1460, 1410, 805, 760, 720.

#### 35 Example 194

##### Synthesis of 3-[3-(4-pyridylthio)propyl]quinazoline-2(1H)-thion-4(3H)-one

Under nitrogen atmosphere, to a solution of 1.48 g (5.15 mmol) of 4-[3-(2-aminobenzoylamino)propylthio]pyridine in 30 ml of tetrahydrofuran, 1.84 g (10.3 mmol) of 1,1'-thiocarbonyldiimidazole was added, and the mixture was stirred at room temperature for 64 hours. The solvent was distilled off and the residue was washed with chloroform/ether to give 1.16 g of the desired product (68.5% yield, pale brown crystals).

40 NMR (200 MHz, DMSO- $d_6$ )  $\delta$ : 2.09 (2H, quint., J=7.6 Hz), 3.16 (2H, t, J=7.2 Hz), 4.56 (2H, t, J=7.6 Hz), 7.27 (2H, dd, J=1.6, 4.6 Hz), 7.30-7.42 (2H, m), 7.74 (1H, ddd, J=1.5, 7.0, 7.2 Hz), 7.67 (1H, dd, J=1.4, 8.0 Hz), 8.36 (2H, dd, J=1.6, 4.6 Hz).

45 IR (KBr)  $cm^{-1}$ : 2920, 2850, 1685, 1625, 1585, 1410, 1140, 760, 720.

#### Example 195

##### 50 Synthesis of 3-[4-(2-pyridylthio)butyl]quinazoline-2,4(1H,3H)-dione

Under nitrogen atmosphere, to a solution of 452 mg (1.5 mmol) of 2-[4-(2-aminobenzoylamino)butylthio]pyridine in 20 ml of tetrahydrofuran, 486 mg (3.0 mmol) of 1,1'-carbonyldiimidazole was added, and the mixture was stirred at room temperature for 16 hours. The solvent was distilled off and the residue was dissolved in chloroform. The solution was washed with water and dried. The solvent was distilled off and the residue was  
55 recrystallized from chloroform/ether to give 337 mg of the desired product (68.8% yield, white crystals).

NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 1.75-1.99 (4H, m), 3.25 (2H, t, J=6.8 Hz), 4.15 (2H, t, J=7.0 Hz), 6.94 (1H, ddd, J=1.2, 5.0, 7.2 Hz), 7.12-7.23 (3H, m), 7.44 (1H, ddd, J=2.0, 7.8, 8.0 Hz), 7.96 (1H, m), 8.13 (1H, dd, J=1.4,

8.0 Hz), 8.39 (1H, m), 10.32 (1H, s).  
IR (KBr)  $\text{cm}^{-1}$ : 3190, 1720, 1635, 765.

#### Example 196

##### Synthesis of 3-[4-(2-pyridylthio)butyl]quinazoline-2(1H)-thion-4(3H)-one

In a solution of 1.94 g (5.18 mmol) of 2-[4-(2-aminobenzoylamino)butylthio]pyridine dihydrochloride in 10 ml of methanol, 6.5 ml (13.0 mmol) of 2 N aqueous sodium hydroxide was added, and the mixture was stirred at room temperature for 1 hour. Water was added to the reaction mixture, and the mixture was extracted with chloroform. The extract was dried and the solvent was distilled off. The resulting free amine was used in the subsequent reaction without further purification.

Under nitrogen atmosphere, to a solution of the above free amine in 20 ml of tetrahydrofuran, 1.43 g (8.0 mmol) of 1,1'-thiocarbonyldiimidazole was added, and the mixture was stirred at room temperature for 16 hours. The solvent was distilled off and the residue was dissolved in chloroform. The solution was washed with water and dried. The solvent was distilled off and the residue was recrystallized from chloroform/ether to give 0.856 g (62.2% yield, pale brown solid).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.76-2.08 (4H, m), 3.25 (2H, t,  $J=7.0$  Hz), 4.56 (2H, t,  $J=7.8$  Hz), 6.95 (1H, ddd,  $J=1.0, 5.0, 7.2$  Hz), 7.09-7.18 (2H, m), 7.27-7.35 (1H, m), 7.45 (1H, ddd,  $J=1.4, 7.4, 8.0$  Hz), 7.61-7.70 (1H, m), 8.13 (1H, dd,  $J=1.6, 8.0$  Hz), 8.39-8.43 (1H, m), 10.82 (1H, s).

#### Example 197

##### Synthesis of 1,3-bis[3-(4-pyridylthio)propyl]quinazoline-2,4(1H,3H)-dione dihydrochloride

###### i) Synthesis of 1,3-bis[3-(4-pyridylthio)propyl]quinazoline-2,4(1H,3H)-dione

To a solution of 1.62 g (10 mmol) of benzoylene urea and 1.88 g (10 mmol) of 4-(3-chloropropylthio)pyridine in 50 ml of dimethylformamide, 1.65 ml (11 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/ethanol = 25 : 1 to 10 : 1 to 2 : 1). First, 0.973 g of 3-[3-(4-pyridylthio)propyl]quinazoline-2,4-(1H,3H)-dione (31.1% yield, pale yellow crystals) was obtained, and then, 0.487 g of the desired product was obtained (10.4% yield, yellow oil).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.04-2.24 (4H, m), 3.02-3.16 (4H, m), 4.27-4.35 (4H, m), 7.08-7.30 (6H, m), 7.62 (1H, ddd,  $J=1.8, 7.0, 7.2$  Hz), 8.23 (1H, dd,  $J=1.6, 8.0$  Hz), 8.35-8.41 (4H, m).

###### ii) Synthesis of 1,3-bis[3-(4-pyridylthio)propyl]quinazoline-2,4(1H,3H)-dione dihydrochloride

To a solution of 150 mg (0.323 mmol) of the above free amine in 15 ml of methanol, 30 ml of 10% hydrochloric acid/methanol was added, and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off and the residue was purified by recrystallization (solvent: ethanol/ether) to give 80.0 mg of the desired product (46.1% yield, pale yellow crystals).

NMR (200 MHz,  $\text{D}_2\text{O}$ )  $\delta$ : 2.11-2.30 (4H, m), 3.27-3.50 (4H, m), 4.10-4.40 (4H, m), 7.32-7.48 (2H, m), 7.73-7.82 (5H, m), 8.02 (1H, t,  $J=7.0$  Hz), 8.39 (4H, d,  $J=6.6$  Hz).

#### Example 198

##### Synthesis of 1,3-bis[4-(2-pyridylthio)butyl]quinazoline-2,4(1H,3H)-dione

To a solution of 1.62 g (10 mmol) of benzoylene urea and 2.02 g (10 mmol) of 2-(4-chlorobutylthio)pyridine in 50 ml of dimethylformamide, 1.65 ml (11 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: hexane/ethyl acetate = 2 : 1 to 1 : 2). First, 221 mg of the desired product was obtained (4.6% yield, yellow oil), and then, 292 mg of 3-[4-(2-pyridylthio)butyl]quinazoline-2,4(1H,3H)-dione was obtained (8.9% yield, white crystals).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.76-1.94 (8H, m), 3.18-3.29 (4H, m), 4.08-4.20 (4H, m), 6.90-7.00 (2H, m),

7.12-7.23 (4H, m), 7.39-7.51 (2H, m), 7.63 (1H, ddd, J=1.6, 7.0, 7.4 Hz), 8.22 (1H, dd, J=1.8, 8.0 Hz), 8.37-8.42 (2H, m).

#### Example 199

Synthesis of 1-(4-pyridylthio)methyl-3-[4-(4-pyridylthio)butyl]quinazoline-2,4(1H,3H)-dione dihydrochloride

i) Synthesis of 1-(4-pyridylthio)methyl-3-[4-(4-pyridylthio)butyl]quinazoline-2,4(1H,3H)-dione

To a solution of 491 mg (1.5 mmol) of 3-[4-(4-pyridylthio)butyl]quinazoline-2,4(1H,3H)-dione and 287 mg (1.8 mmol) of 4-chloromethylthiopyridine in 15 ml of dimethylformamide, 0.27 ml (1.8 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane = 2 : 1 to 4 : 1 to ethyl acetate) to give 0.315 g of the desired product (46.7% yield, colorless oil).

NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.68-1.90 (4H, m), 3.02 (2H, t, J=7.0 Hz), 4.10 (2H, t, J=7.2 Hz), 5.72 (2H, s), 7.10 (2H, dd, J=1.5, 4.8 Hz), 7.20 (1H, d, J=8.6 Hz), 7.33 (1H, dt, J=1.0, 7.0 Hz), 7.42 (2H, dd, J=1.6, 4.6 Hz), 7.72 (1H, ddd, J=1.8, 7.0, 7.4 Hz), 8.25 (1H, dd, J=1.4, 8.0 Hz), 8.35 (2H, dd, J=1.4, 4.8 Hz), 8.48 (2H, dd, J=1.6, 4.6 Hz).

IR (neat) cm<sup>-1</sup>: 3030, 2960, 1705, 1660, 1575, 1480, 1400, 1260, 805, 760, 710.

ii) Synthesis of 1-(4-pyridylthio)methyl-3-[4-(4-pyridylthio)butyl]quinazoline-2,4(1H,3H)-dione dihydrochloride

To a solution of 200 mg (0.44 mmol) of the above free amine in 10 ml of methanol, 50 ml of 10% hydrochloric acid/methanol was added, and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off and the residue was purified by recrystallization (solvent: ethanol/ether) to give 183 mg of the desired product (78.8% yield, white crystals), mp. 148-150°C.

#### Example 200

Synthesis of 1,3-bis[4-(4-pyridylthio)butyl]quinazoline-2(1H)-thion-4(3H)-one dihydrochloride

i) Synthesis of 1,3-bis[4-(4-pyridylthio)butyl]quinazoline-2(1H)-thion-4(3H)-one

To a solution of 515 mg (1.5 mmol) of 3-[4-(4-pyridylthio)butyl]quinazoline-2(1H)-thion-4(3H)-one and 332 mg (1.65 mmol) of 4-(4-chlorobutylthio)pyridine in 15 ml of dimethylformamide, 0.25 ml (1.65 mmol) of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by flash column chromatography (eluent: ethyl acetate/ethanol = 25 : 1 to 10 : 1) to give 0.694 mg of the desired product (97.1% yield; colorless oil).

NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.78-2.06 (8H, m), 3.02-3.11 (4H, m), 3.34 (2H, t, J=7.0 Hz), 4.17 (2H, t, J=7.0 Hz), 7.12 (4H, d, J=5.4 Hz), 7.35-7.52 (2H, m), 7.69 (1H, ddd, J=1.4, 7.0, 7.0 Hz), 8.22 (1H, dd, J=1.4, 8.0 Hz), 8.40 (4H, s).

IR (neat) cm<sup>-1</sup>: 2960, 1700, 1655, 1610, 1480, 1400, 1100, 760, 695.

ii) Synthesis of 1,3-bis[4-(4-pyridylthio)butyl]quinazoline-2(1H)-thion-4(3H)-one dihydrochloride

To a solution of 449 mg (0.94 mmol) of the free amine in 30 ml of methanol, 100 ml of 10% hydrochloric acid/methanol was added, and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off and the residue was purified by recrystallization (solvent: ethanol/ether) to give 450 mg of the desired product (86.9% yield, white crystals), mp. 87-89°C.

#### Example 201

Synthesis of 1,3-bis[3-(4-pyridylthio)propyl]quinazoline-2(1H)-thion-4(3H)-one

To a solution of 494 mg (1.5 mmol) of 3-[4-(4-pyridylthio)propyl]quinazoline-2(1H)-thion-4(3H)-one and 338 mg (1.8 mmol) of 4-(3-chloropropylthio)pyridine in 15 ml of dimethylformamide, 0.27 ml (1.8 mmol) of 1,8-dia-

zabicyclo-[5.4.0]-7-undecene was added, and the mixture was stirred at room temperature for 3 hours and at 80°C for 16 hours. After cooling, the solvent was distilled off and the residue was dissolved in chloroform. The solution was washed with water and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/ethanol = 25 : 1 to 10 : 1 to 5 : 1) to give 0.73 g of the desired product (100% yield, yellow oil).

NMR (200 MHz, CDCl<sub>3</sub>) δ: 2.21 (4H, quint., J=6.8 Hz), 3.12 (4H, q, J=7.2 Hz), 3.42 (2H, t, J=7.0 Hz), 4.30 (2H, t, J=7.2 Hz), 7.12 (4H, s), 7.35-7.51 (2H, m), 7.70 (1H, ddd, J=1.6, 7.0, 7.2 Hz), 8.20 (1H, dd, J=1.6, 7.8 Hz), 8.38 (4H, s).

## Example 202

Synthesis of 1,3-bis[4-(4-pyridylthio)butyl]-5,5-dimethylhydantoin dihydrochloride

### i) Synthesis of 1,3-bis[4-(4-pyridylthio)butyl]-5,5-dimethylhydantoin

To a suspension of 96 mg (2.4 mmol) of 60% sodium hydride (oily) in 15 ml of dimethylformamide, 587 mg (2.0 mmol) of 3-[4-(4-pyridylthio)butyl]-5,5-dimethylhydantoin was added, and the mixture was stirred at room temperature for 10 minutes. To this reaction mixture, 807 mg (4.0 mmol) of 4-(4-chlorobutylthio)pyridine was added with stirring under ice-cooling, and the mixture was stirred at 80°C for 16 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate/ethanol = 10 : 1) to give 0.74 g of the desired product (80.7% yield, yellow oil).

NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.37 (6H, s), 1.68-1.88 (8H, m), 2.98-3.07 (4H, m), 3.29 (2H, t, J=7.0 Hz), 3.55 (2H, t, J=6.6 Hz), 7.12 (4H, d, J=4.6 Hz), 8.39 (4H, s).

IR (neat) cm<sup>-1</sup>: 3030, 2935, 1760, 1700, 1575, 1455, 800, 710.

### ii) Synthesis of 1,3-bis[4-(4-pyridylthio)butyl]-5,5-dimethylhydantoin dihydrochloride

To a solution of 0.68 g (1.48 mmol) of the above free amine in 30 ml of methanol, 50 ml of 10% hydrochloric acid/methanol was added, and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off to give 0.91 g of the desired product (100% yield, yellow oil).

NMR (200 MHz, D<sub>2</sub>O) δ: 1.40 (6H, s), 1.76-1.88 (8H, m), 3.23-3.32 (4H, m), 3.35-3.42 (2H, m), 3.57 (2H, t, J=6.2 Hz), 7.80 (4H, dd, J=1.4, 7.2 Hz), 8.42 (4H, d, J=7.0 Hz).

## Example 203

Synthesis of 1,2-bis[N-(4-(4-pyridylthio)butyl)-N-propionylamino]benzene dihydrochloride

### i) Synthesis of 1,2-dipropionylaminobenzene

To a solution of 3.24 g (30 mmol) of O-phenylenediamine in 9.7 ml (120 mmol) of pyridine, 11.54 ml (90 mmol) of propionic anhydride was added at room temperature, and the mixture was stirred for 16 hours. The resulting precipitate was filtered and washed with ether, followed by drying to give 5.24 g of the desired product (80.1% yield, white crystals).

NMR (200 MHz, DMSO-d<sub>6</sub>) δ: 1.09 (6H, t, J=7.8 Hz), 2.35 (4H, q, J=7.6 Hz), 7.12 (2H, dd, J=3.4, 6.0 Hz), 7.51 (2H, dd, J=3.4, 6.0 Hz), 9.25 (2H, s).

### ii) Synthesis of 1,2-bis[N-(4-(4-chlorobutyl)-N-propionylamino]benzene

To a suspension of 3.27 g (15 mmol) of 1,2-dipropionylaminobenzene, 4.32 ml (37.5 mmol) of 4-bromo-1-chlorobutane, and 0.96 g (3.0 mmol) of tetrabutylammonium bromide in 25 ml of toluene, 5.6 ml of 50% aqueous sodium hydroxide was added at room temperature, and the mixture was stirred for 16 hours. The organic layer was separated, washed with saturated aqueous sodium chloride, and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: hexane/ethyl acetate = 2 : 1 to 1 : 1 to 1 : 2 to 1 : 4) to give 0.76 g of the desired product (12.6% yield, white crystals).

NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.09 (6H, t, J=7.8 Hz), 1.58-1.90 (10H, m), 2.07-2.26 (2H, m), 2.69-2.83 (2H, m), 3.51 (4H, t, J=5.5 Hz), 4.24-4.40 (2H, m), 7.20 (2H, dd, J=3.6, 6.0 Hz), 7.43 (2H, dd, J=3.6, 6.0 Hz).

## iii) Synthesis of 1,2-bis[N-[4-(4-pyridylthio)butyl]-N-propionylamino]benzene

To a solution of 525 mg (4.7 mmol) of 4-mercaptopyridine and 265 mg (4.7 mmol) of potassium hydroxide in 20 ml of dimethyl sulfoxide, 760 mg (1.89 mmol) of 1,2-bis[N-(4-chlorobutyl)-N-propionylamino]benzene was added at room temperature, and the mixture was stirred for 2 hours. The reaction mixture was poured into water and the mixture was extracted with ethyl acetate. The extract was dried and the solvent was distilled off. The residue was purified by column chromatography (eluent: ethyl acetate to ethyl acetate/ethanol = 20 : 1 to 10 : 1 to 5 : 1) to give 0.84 g of the desired product (81.0% yield, pale yellow crystals).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.62-1.74 (8H, m), 1.82 (6H, s), 2.84-2.99 (6H, m), 2.84-2.99 (6H, m), 4.22-4.38 (2H, m), 7.08 (4H, d,  $J=5.8\text{ Hz}$ ), 7.14 (2H, dd,  $J=3.6, 5.8\text{ Hz}$ ), 7.42 (2H, dd,  $J=3.6, 5.8\text{ Hz}$ ), 8.38 (4H, s).

## iv) Synthesis of 1,2-bis[N-[4-(4-pyridylthio)butyl]-N-propionylamino]benzene dihydrochloride

To a solution of 840 mg (1.53 mmol) of 1,2-bis[N-[4-(4-pyridylthio)butyl]-N-propionylamino]benzene in 20 ml of methanol, 80 ml of 10% hydrochloric acid/methanol was added, and the mixture was stirred for 30 minutes. The solvent was distilled off and the residue was recrystallized from ethanol/ether to give 707 mg of the desired product (74.1% yield, pale yellow crystals).

NMR (200 MHz,  $\text{D}_2\text{O}$ )  $\delta$ : 0.95 (3H, t,  $J=7.2\text{ Hz}$ ), 1.80-1.15 (3H, m), 1.62-1.95 (10H, m), 2.10-2.30 (2H, m), 2.74-2.90 (2H, m), 3.10-3.20 (4H, m), 4.04-4.36 (2H, m), 7.22-7.52 (4H, m), 7.69-7.73 (4H, m), 8.32-8.37 (4H, m).

Reference Example 1

## Synthesis of 4-[3-(t-butoxycarbonylamino)propylsulfinyl]pyridine

To a solution of 4.03 g (15.0 mmol) of 4-[3-(t-butoxycarbonylamino)propylthio]pyridine in 100 ml of methylene chloride, 3.05 g (15.0 mmol) of m-chloroperbenzoic acid was added with stirring under ice-cooling, and the mixture was stirred at the same temperature for 1 hour. The reaction mixture was washed two times with saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/ethanol = 10 : 1) to give 3.37 g of the desired compound (78.9% yield, colorless crystals).

NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.43 (9H, s), 1.50-2.30 (2H, m), 2.60-3.10 (2H, m), 3.26 (2H, m), 4.84 (1H, br), 7.54 (2H, m), 8.78 (2H, m).

Reference Example 2

## Synthesis of 4-[3-(t-butoxycarbonylamino)propylsulfonyl]pyridine

To a solution of 4.03 g (15.0 mmol) of 4-[3-(t-butoxycarbonylamino)propylthio]pyridine in 100 ml of methylene chloride, 6.70 g (33.0 mmol) of m-chloroperbenzoic acid was added with stirring under ice-cooling, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was washed two times with saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate) to give 3.68 g of the desired compound (81.6% yield, colorless crystals).

NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.40 (9H, s), 1.75-2.13 (2H, m), 3.06-3.38 (4H, m), 4.70 (1H, br), 7.75 (2H, m), 8.90 (2H, m).

Reference Example 3

## Synthesis of 4-(4-chlorobutylthio)pyridine

To a suspension of 33.35 g (0.30 mol) of 4-mercaptopyridine and 51.44 g (0.30 mol) of 1-bromo-4-chlorobutane in 500 ml of ethanol, 41.9 ml (0.30 mol) of triethylamine was added, and the mixture was stirred at room temperature for 5 hours. The solvent was distilled off and chloroform was added to the residue. The mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by column chromatography (eluent: ethyl acetate/n-hexane = 1 : 1) to give 54.27 g of the desired compound (89.7% yield, colorless oil).

NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.92 (4H, m), 3.02 (2H, t,  $J=6.8\text{ Hz}$ ), 3.59 (2H, t,  $J=6.2\text{ Hz}$ ), 7.12 (2H, dd,

J=4.6, 1.6 Hz), 8.40 (2H, dd, J=4.0, 1.6 Hz).

#### Reference Example 4

##### 5 Synthesis of 4-(3-chloropropylthio)pyridine

The desired compound was synthesized in the same manner as described in Reference Example 3.

NMR (200 MHz, CDCl<sub>3</sub>) δ: 2.17 (2H, m), 3.17 (2H, t, J=7 Hz), 3.70 (2H, t, J=6 Hz), 7.14 (2H, dd, J=4.6, 1.6 Hz), 8.42 (2H, dd, J=4.6, 1.6 Hz).

10

#### Reference Example 5

##### Synthesis of 4-(2-chloroethylthio)pyridine

15 The desired compound was synthesized in the same manner as described in Reference Example 3.

NMR (200 MHz, CDCl<sub>3</sub>) δ: 3.34 (2H, t, J=8.4 Hz), 3.70 (2H, t, J=8.0 Hz), 7.15 (2H, dd, J=1.6, 4.4 Hz), 8.45 (2H, dd, J=1.4, 4.4 Hz).

#### Reference Example 6

20

##### Synthesis of 2-(4-chlorobutylthio)pyridine

This compound was synthesized by the same method as used in Reference Example 3.

25 NMR (200 MHz, CDCl<sub>3</sub>) δ: 1.70-2.05 (4H, m), 3.21 (2H, t, J=6.8 Hz), 3.58 (2H, t, J=6.2 Hz), 6.98 (1H, ddd, J=1.2, 5.0, 7.4 Hz), 7.17 (1H, d, J=8.0 Hz), 7.48 (1H, ddd, J=1.8, 7.2, 7.8 Hz), 8.40-8.45 (1H, m).

#### Reference Example 7

##### Synthesis of 4-[3-(2-aminobenzoylamino)propylthio]pyridine dihydrochloride

30

##### i) Synthesis of 4-[3-(2-aminobenzoylamino)propylthio]pyridine

35 To a solution of 4.82 g (20 mmol) of 4-(3-aminopropylthio)pyridine dihydrochloride in 20 ml of methanol, 25 ml (50 mmol) of 2 N aqueous sodium hydroxide was added, and the mixture was stirred at room temperature for 1 hour. Water was added to the reaction mixture and the mixture was extracted with chloroform. The extract was dried and the solvent was distilled off. The resulting free amine was used in the subsequent reaction without further purification.

40 To a solution of the above free amine in 30 ml of dimethylformamide, 3.26 g (20 mmol) of isatoic anhydride was added, and the mixture was stirred at 80°C for 30 minutes. After cooling, the solvent was distilled off. The residue was dissolved in chloroform, and the solution was washed with aqueous sodium bicarbonate and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: chloroform/methanol = 20 : 1) to give 5.49 g of the desired product (95.5% yield, yellow oil).

45 NMR (200 MHz, CDCl<sub>3</sub>) δ: 2.04 (2H, quint., J=7.0 Hz), 3.08 (2H, t, J=7.2 Hz), 3.58 (2H, q, J=6.2 Hz), 5.51 (2H, s), 6.25 (1H, s), 6.6-6.71 (2H, m), 7.12 (2H, dd, J=1.4, 4.6 Hz), 7.18-7.32 (2H, m), 8.39 (2H, dd, J=1.6, 4.8 Hz).

##### ii) Synthesis of 4-[3-(2-aminobenzoylamino)propylthio]pyridine dihydrochloride

50 To a solution of 2.39 g (8.32 mmol) of the above free amine in 30 ml of methanol, 200 ml of 10% hydrochloric acid/methanol was added, and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off and the residue was purified by recrystallization (solvent: ethanol/ether) to give 2.23 g of the desired product (74.4% yield, white crystals).

NMR (200 MHz, D<sub>2</sub>O) δ: 2.15 (2H, quint., J=7.0 Hz), 3.36 (2H, t, J=7.2 Hz), 3.60 (2H, t, J=6.6 Hz), 7.45-7.59 (2H, m), 7.65-7.74 (1H, m), 7.79-7.85 (3H, m), 8.41 (2H, d, J=7.4 Hz).

55 IR (KBr) cm<sup>-1</sup>: 1625, 1600, 1480, 1120, 815, 100, 740.

Reference Example 8

## Synthesis of 2-[4-(2-aminobenzoylamino)butylthio]pyridine dihydrochloride

## 5 i) Synthesis of 2-[4-(2-aminobenzoylamino)butylthio]pyridine

To a suspension of 6.25 g (20 mmol) of 2-(4-phthalimidobutylthio)pyridine in 150 ml of ethanol, 2.91 ml (60 mmol) of hydrazine monohydrate was added, and the mixture was heated under reflux for 2 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with chloroform. The extract was dried and the solvent was distilled off. The resulting free amine was used in the subsequent reaction without further purification.

To a solution of the above free amine in 30 ml of dimethylformamide, 3.26 g (20 mmol) of isatoic acid anhydride was added, and the mixture was stirred at 80°C for 1 hour. After cooling, the solvent was distilled off. The residue was dissolved in chloroform, and the solution was washed with aqueous sodium bicarbonate and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: hexane/ethyl acetate = 1 : 1) to give 2.61 g (43.5% yield, yellow oil).

NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.70-1.82 (4H, m), 3.22 (2H, t, J=7.0 Hz), 3.48 (2H, q, J=6.6 Hz), 5.50 (2H, s), 6.29 (1H, s), 6.57-6.70 (2H, m), 6.95 (1H, ddd, J=1.2, 4.8, 7.4 Hz), 7.15-7.31 (3H, m), 7.46 (1H, dt, J=1.8, 7.4 Hz), 8.37 (1H, dd, J=1.2, 5.2 Hz).

## 20 ii) Synthesis of 2-[4-(2-aminobenzoylamino)butylthio]pyridine dihydrochloride

To a solution of 606 mg (2.01 mmol) of the above free amine in 10 ml of methanol, 50 ml of 10% hydrochloric acid and methanol was added, and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off and the residue was purified by recrystallization (solvent: isopropylalcohol/methanol/ether) to give 710 mg of the desired product (94.5% yield, white crystals).

NMR (200 MHz, D<sub>2</sub>O)  $\delta$ : 1.84-1.92 (4H, m), 3.37-3.49 (4H, m), 7.42-7.54 (2H, m), 7.61-7.74 (3H, m), 7.91 (1H, d, J=8.4 Hz), 8.29 (1H, dt, J=1.6, 8.0 Hz), 8.49 (1H, d, J=5.8 Hz).

IR (KBr) cm<sup>-1</sup>: 1645, 1590, 1545, 1320, 1140, 760.

30 Reference Example 9

## Synthesis of 4-[4-(2-aminobenzoylamino)butylthio]pyridine dihydrochloride

## 35 i) Synthesis of 4-[4-(2-aminobenzoylamino)butylthio]pyridine

To a suspension of 6.25 g (20 mmol) of 4-(4-phthalimidobutylthio)pyridine in 150 ml of ethanol, 2.91 ml (60 mmol) of hydrazine monohydrate was added, and the mixture was heated under reflux for 2 hours. After cooling, water was added to the reaction mixture, and the mixture was extracted with chloroform. The extract was dried and the solvent was distilled off. The resulting free amine was used in the subsequent reaction without further purification.

To a solution of the above free amine in 30 ml of dimethylformamide, 3.26 g (20 mmol) of isatoic anhydride was added, and the mixture was stirred at 80°C for 1 hour. After cooling, the solvent was distilled off and the residue was dissolved in chloroform. The solution was washed with aqueous sodium bicarbonate and dried. The solvent was distilled off and the residue was purified by column chromatography (eluent: hexane/ethyl acetate = 1 : 1) to give 1.74 g of the desired product (28.9% yield, pale orange solid).

NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.76-1.83 (4H, m), 3.03 (2H, t, J=7.0 Hz), 3.46 (2H, q, J=6.2 Hz), 5.49 (2H, s), 6.18 (1H, s), 6.58-6.70 (2H, m), 7.10 (2H, dd, J=1.6, 4.6 Hz), 7.15-7.29 (2H, m), 8.37 (2H, dd, J=1.4, 6.2 Hz).

## 50 ii) Synthesis of 2-[4-(2-aminobenzoylamino)butylthio]pyridine dihydrochloride

To a solution of 1.74 g (5.77 mmol) of the above free amine in 30 ml of methanol, 100 ml of 10% hydrochloric acid and methanol was added and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off and the residue was purified by recrystallization (solvent: ethanol/ether) to give 1.68 g of the desired product (77.8% yield, white crystals).

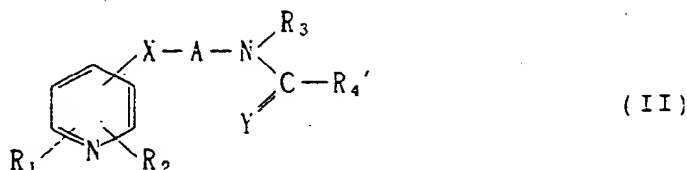
NMR (200 MHz, D<sub>2</sub>O)  $\delta$ : 1.85-1.90 (4H, m), 3.31 (2H, t, J=6.8 Hz), 3.47 (2H, t, J=6.4 Hz), 7.45-7.56 (2H, m), 7.64-7.73 (2H, m), 7.79 (2H, d, J=7.2 Hz), 8.37 (2H, d, J=7.2 Hz).



IR (KBr)  $\text{cm}^{-1}$ : 3315, 1620, 1540, 1110, 800, 754.

# Claims

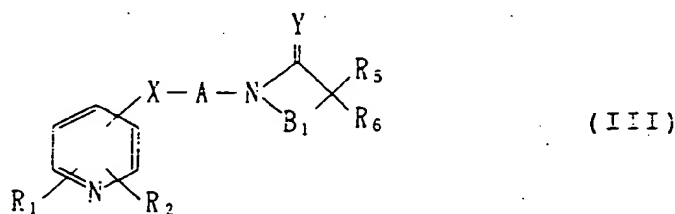
1. A pyridine derivative of the formula (II):



wherein  $R_1$  and  $R_2$  are the same or different and are a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, hydroxy group, nitro group, cyano group, amino group, carbamoyl group, an acylamino group, a lower alkylamino group, a lower alkenylamino or an aralkylamino group, X is an oxygen atom or  $-\text{S}(\text{O})_n-$ , wherein n is 0, 1 or 2, A is a bivalent  $\text{C}_{1-15}$  hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom,  $R_3$  is a hydrogen atom or an optionally substituted hydrocarbon residue,  $R_4'$  is (1) a  $\text{C}_{2-30}$  alkyl group, (2) a  $\text{C}_{2-30}$  alkenyl group, (3) a lower alkyl group substituted with a halogen atom, an aryl group or a heterocyclic group, (4) a lower alkenyl group substituted with a halogen atom or a heterocyclic group, (5) an optionally substituted aralkyl group, (6) an optionally substituted aryl group or (7) an optionally substituted monocyclic or bicyclic heterocyclic group, or a salt or solvate thereof.

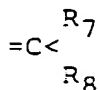
2. A pyridine derivative according to claim 1,  $R_1$  and  $R_2$  are the same or different and are a hydrogen atom, amino group or an acylamino, X is an oxygen or sulfur atom, A is a bivalent  $\text{C}_{1-6}$  hydrocarbon residue, Y is an oxygen atom,  $R_3$  is a hydrogen atom, an optionally substituted aralkyl group or an optionally substituted aryl group,  $R_4'$  is a  $\text{C}_{2-30}$  alkyl group, a halogeno lower alkyl group, an optionally substituted aryl group or an optionally substituted monocyclic or bicyclic heterocyclic group.
3. A pyridine derivative according to claim 2, wherein A is a  $\text{C}_{1-4}$  alkylene.
4. The pyridine derivative according to claim 1 selected from: 4-[3-(N-benzyl-N-trifluoroacetyl-amino)propylthio]pyridine hydrochloride; 4-[2-(thianaphthene-2-carbonylamino)ethylthio]pyridine; and 1,2-bis[N-[4-(4-pyridylthio)butyl]-N-propionylamino]benzene dihydrochloride.

5. A pyridine derivative of the formula (III):

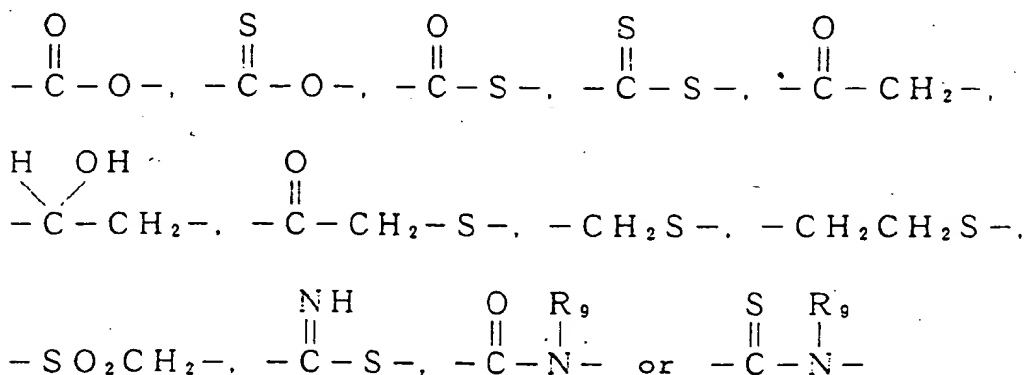


wherein  $R_1$  and  $R_2$  are the same or different and are a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, hydroxy group, nitro group, cyano group, amino group, carbamoyl group, an acylamino group, a lower alkylamino group, a lower alkenylamino group or an aralkylamino group, X is an oxygen atom or  $-\text{S}(\text{O})_n-$ , wherein n is 0, 1 or 2; A is a bivalent  $\text{C}_{1-15}$  hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom,  $R_5$  and  $R_6$  are the same or different and are a hydrogen atom, a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl group or an optionally sub-

stituted aryl group, or  $R_5$  and  $R_6$  are joined to form a group of the formula:



wherein  $R_7$  and  $R_8$  are the same or different and are a hydrogen atom, a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl group, an optionally substituted aryl group or an optionally substituted monocyclic or a bicyclic heterocyclic group, or  $R_7$  and  $R_8$  are linked together to form a ring.  $B_1$  is  $-(CH_2)_p-$ , wherein  $p$  is an integer of 1 to 4, or a group of the formula:



wherein  $R_9$  is a hydrogen atom, an optionally substituted lower alkyl, lower alkenyl or aralkyl group, or a salt or solvate thereof.

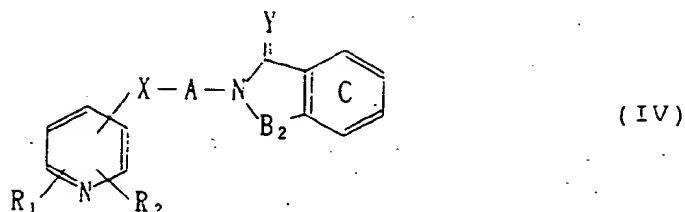
6. A pyridine derivative according to claim 5, wherein  $R_1$  and  $R_2$  are the same or different and are a hydrogen atom, amino group or an acylamino group,  $X$  is an oxygen or sulfur atom,  $Y$  is an oxygen atom,  $A$  is a bi-valent  $C_{1-6}$  hydrocarbon residue,  $R_5$  and  $R_6$  are the same or different and are a hydrogen atom or a lower alkyl, or  $R_5$  and  $R_6$  are joined to form a group of the formula:



wherein  $R_7$  and  $R_8$  are the same or different and are a hydrogen atom, a lower alkyl group, an optionally substituted aralkyl group, an optionally substituted aryl group or an optionally substituted monocyclic or bicyclic heterocyclic group,  $B_1$  is  $-C(=O)-O-$ ,  $-C(=O)-S-$ ,  $-C(=O)-CH_2-$  or  $-C(=O)-NR_9-$ , wherein  $R_9$  is as defined in claim 7.

7. A pyridine derivative according to claim 6, wherein  $R_1$  and  $R_2$  are a hydrogen atom,  $A$  is a  $C_{1-4}$  alkylene,  $B_1$  is  $-C(=O)-S-$  or  $-C(=O)-NR_9-$ .
8. The pyridine derivative according to claim 5 selected from: 4-[4-(5-benzylidene-2,4-thiazolidinedione)butylthio]pyridine;  
 4-[4-[5-(4-chlorobenzylidene)-2,4-thiazolidinedione]butylthio]pyridine;  
 4-[4-(5-(2-thienylmethylene)-2,4-thiazolidinedione)butylthio]pyridine;  
 4-[4-(5-propylmethylene-2,4-thiazolidinedione)butylthio]pyridine;  
 4-(5,5-dimethyloxazolidine-2,4-dione)methylthiopyridine;  
 4-[4-[5-(4-pyridyl)methylene-2,4-thiazolidinedione]butylthio]pyridine;  
 4-[4-[5-(3-pyridyl)methylene-2,4-thiazolidinedione]butylthio]pyridine; and  
 4-[4-(5-nonylmethylene-2,4-thiazolidinedione)butylthio]pyridine hydrochloride.

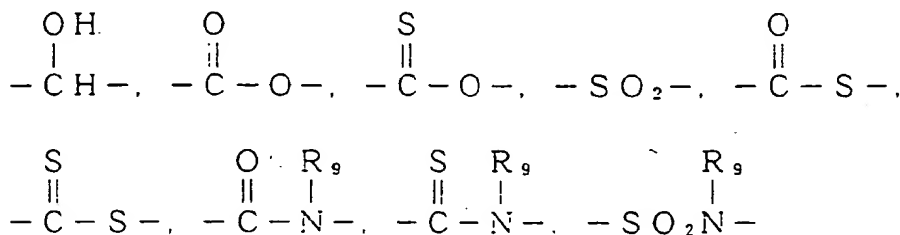
9. A pyridine derivative of the formula (IV):



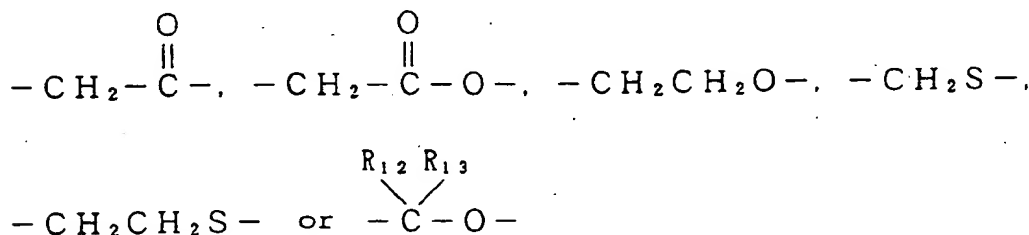
wherein  $R_1$  and  $R_2$  are the same or different and are a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, hydroxy group, nitro group, cyano group, amino group, carbamoyl group, an acylamino group, a lower alkylamino group, a lower alkenylamino group or an aralkylamino group, X is an oxygen atom or  $-S(O)_n-$ , wherein n is 0, 1 or 2, A is a bivalent  $C_{1-15}$  hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom, a group of the formula:



is an optionally substituted benzene ring,  $B_2$  is  $-(CH_2)_p-$ , wherein p is an integer of 1 to 4, or a group of the formula:



wherein  $R_9$  is a hydrogen atom, an optionally substituted lower alkyl, lower alkenyl or aralkyl group, or a group of the formula:



wherein  $R_{12}$  and  $R_{13}$  are the same or different and are a hydrogen atom, a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl group or an aryl group, or  $R_{12}$  and  $R_{13}$  may be linked together to form a ring, or a salt or solvate thereof.

10. A pyridine derivative according to claim 9, wherein  $R_1$  and  $R_2$  are the same or different and are a hydrogen atom, amino group or an acylamino group, X is an oxygen or sulfur atom, A is a bivalent  $C_{1-8}$  hydrocarbon residue, Y is an oxygen atom,  $B_2$  is  $-(CH_2)_p-$ ,  $-(HO)-CH-$ ,  $-C(=O)-O-$ ,  $-C(=S)-O-$ ,  $-SO_2-$ ,  $-C(=O)-NR_9-$  or  $-C(=S)-NR_9-$  wherein p is an integer of 1 to 4,  $R_9$  is a hydrogen atom or an optionally substituted lower alkyl group.

11. A pyridine derivative according to claim 10, wherein  $R_1$  and  $R_2$  are a hydrogen atom, A is a  $C_{1-4}$  alkylene,

B<sub>2</sub> is -CH<sub>2</sub>-, -C(=O)-O-, -C(=S)-O-, -SO<sub>2</sub>-, -C(=O)-NR<sub>9</sub>- or -C(=S)-NR<sub>9</sub>-, and the substituent of the lower alkyl group is pyridylthio group.

12. The pyridine derivative according to claim 9 selected from: 3-[3-(4-pyridylthio)propyl]-2H-1,3-benzoxazine-2-thion-4(3H)-one;

3-[4-(4-pyridylthio)butyl]quinazoline-2,4-(1H,3H)-dione;

1,3-bis[4-(4-pyridylthio)butyl]quinazoline-2,4-(1H,3H)-dione;

3-[4-(4-pyridylthio)butyl]-2H-1,3-benzoxazine-2-thion-4(3H)-one;

4-saccharinmethylthiopyridine;

4-saccharinmethylthiopyridine hydrochloride;

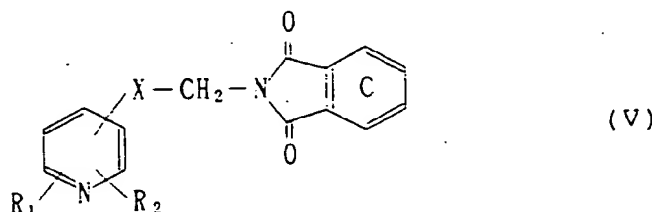
1,3-bis[4-(2-pyridylthio)butyl]quinazoline-2,4(1H,3H)-dione;

1-(4-pyridylthio)methyl-3-[4-(4-pyridylthio)butyl]quinazoline-2,4(1H,3H)-dione dihydrochloride;

and

1,3-bis[4-(4-pyridylthio)butyl]quinazoline-2(1H)-thion-4(3H)-one dihydrochloride.

13. A pyridine derivative of the formula (V):



wherein R<sub>1</sub> and R<sub>2</sub> are the same or different and are a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, hydroxy group, nitro group, cyano group, amino group, carbamoyl group, an acylamino group, a lower alkylamino group, a lower alkenylamino group or an aralkylamino group, X is an oxygen atom or -S(O)<sub>n</sub>-, wherein n is 0, 1 or 2, a group of the formula:



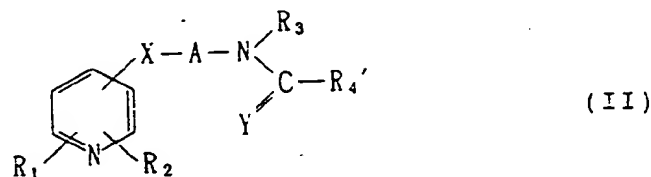
is an optionally substituted benzene ring, or a salt or solvate thereof.

14. A pyridine derivative according to claim 13, wherein R<sub>1</sub> and R<sub>2</sub> are the same or different and are a hydrogen atom, amino group or an acylamino group, X is an oxygen or sulfur atom.

15. A pyridine derivative according to claim 14, wherein R<sub>1</sub> and R<sub>2</sub> are a hydrogen atom.

16. The pyridine derivative according to claim 13 which is 4-(phthalimidomethylthio)pyridine, or 4-(phthalimidomethoxy)pyridine.

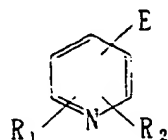
17. A process for producing a pyridine derivative of the formula (II):



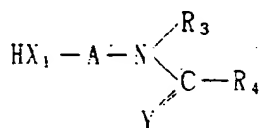
wherein R<sub>1</sub> and R<sub>2</sub> are the same or different and are a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, hydroxy group, nitro group, cyano group, amino group, carbamoyl group, an acylamino group, a lower alkylamino group, a lower alkenylamino or an aralkylamino

group, X is an oxygen atom or  $-S(O)_n-$ , wherein n is 0, 1 or 2, A is a bivalent  $C_{1-15}$  hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom,  $R_3$  is a hydrogen atom or an optionally substituted hydrocarbon atom,  $R_4'$  is (1) a  $C_{2-30}$  alkyl group, (2) a  $C_{2-30}$  alkenyl group, (3) a lower alkyl group substituted with a halogen atom, an aryl group or a heterocyclic group, (4) an optionally substituted aralkyl group, (5) an optionally substituted aryl group or (6) an optionally substituted monocyclic or bicyclic heterocyclic group, or a salt or solvate thereof, which comprises the steps of:

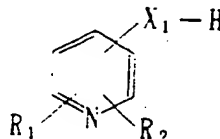
(a) when X is O or S, reacting a compound of the formula:



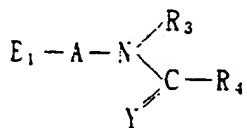
wherein E is a halogen atom and the other symbols are as defined above, with a compound of the formula:



wherein  $X_1$  is O or S and the other symbols are as defined above; or  
(b) when X is O or S, reacting a compound of the formula:

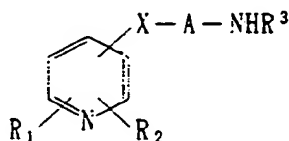


wherein each symbol is as defined above, with a compound of the formula:

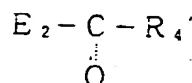


wherein  $E_2$  is a leaving group such as a halogen atom, methanesulfonyloxy, p-toluenesulfonyloxy, etc. and the other symbols are as defined above; or

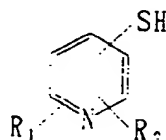
(c) when Y is O, reacting a compound of the formula:



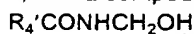
wherein each symbol is as defined above, with a compound of the formula:



wherein  $\text{E}_2$  is a halogen atom,  $\text{O}-\text{C}(=\text{O})-\text{R}_4'$  or  $\text{OH}$  and the other symbols are as defined above; or  
(d) when  $\text{X}$  is  $\text{S}$  and  $\text{A}$  is  $\text{CH}_2$ ,  $\text{R}_3$  is a hydrogen atom and  $\text{Y}$  is  $\text{O}$ , reacting a compound of the formula:

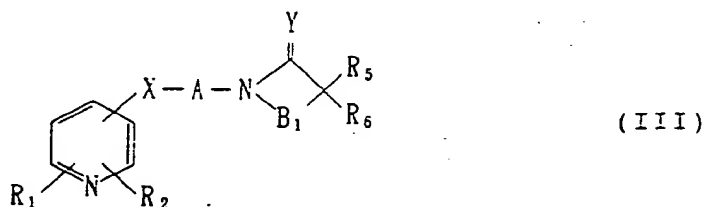


wherein each symbol is as defined above, with a compound of the formula:



wherein each symbol is as defined above.

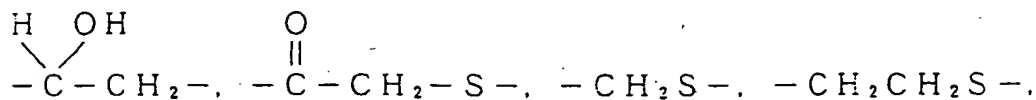
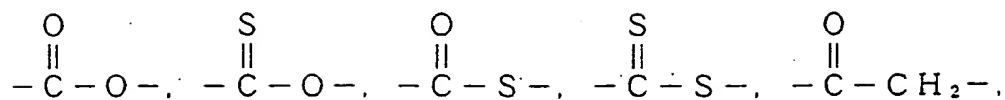
18. A process for producing a pyridine derivative of the formula (III):



wherein  $\text{R}_1$  and  $\text{R}_2$  are the same or different and are a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, hydroxy group, nitro group, cyano group, amino group, carbamoyl group, an acylamino group, a lower alkylamino group, a lower alkenylamino group or an aralkylamino group,  $\text{X}$  is an oxygen atom or  $-\text{S}(\text{O})_n-$ , wherein  $n$  is 0, 1 or 2;  $\text{A}$  is a bivalent  $\text{C}_{1-15}$  hydrocarbon residue whose branched moiety may have a substituent,  $\text{Y}$  is an oxygen or sulfur atom,  $\text{R}_5$  and  $\text{R}_6$  are the same or different and are a hydrogen atom, a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl group or an optionally substituted aryl group, or  $\text{R}_5$  and  $\text{R}_6$  are joined to form a group of the formula:

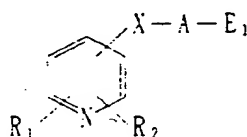


wherein  $\text{R}_7$  and  $\text{R}_8$  are the same or different and are a hydrogen atom, a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl group, an optionally substituted aryl group or an optionally substituted monocyclic or a bicyclic heterocyclic group, or  $\text{R}_7$  and  $\text{R}_8$  are linked together to form a ring,  $\text{B}_1$  is  $-(\text{CH}_2)_p-$ , wherein  $p$  is an integer of 1 to 4, or a group of the formula:

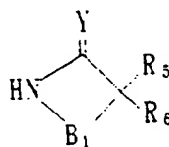


wherein  $\text{R}_9$  is a hydrogen atom, an optionally substituted lower alkyl, lower alkenyl or aralkyl group, or a salt or solvate thereof, which comprises the steps of:

(a) reacting a compound of the formula:

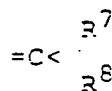


wherein each symbol is as defined above, with a compound of the formula:

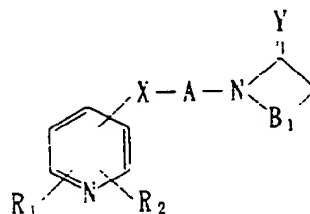


wherein each symbol is as defined above; or

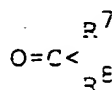
(b) when  $\text{R}_5$  and  $\text{R}_6$  are joined to form the group of the formula:



wherein each symbol is as defined above, reacting a compound of the formula:

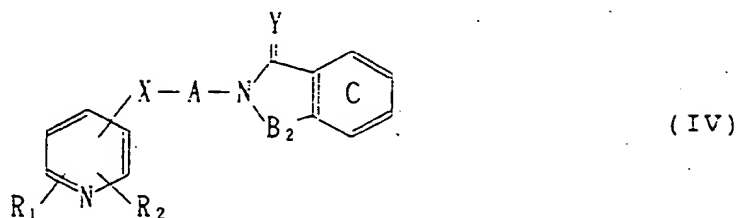


wherein each symbol is as defined above, with a compound of the formula:



wherein each symbol is as defined above.

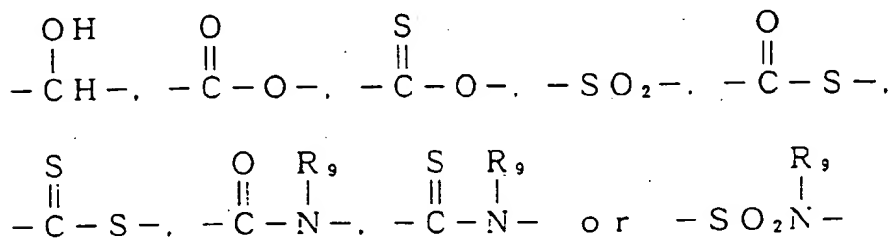
19. A process for producing a pyridine derivative of the formula (IV):



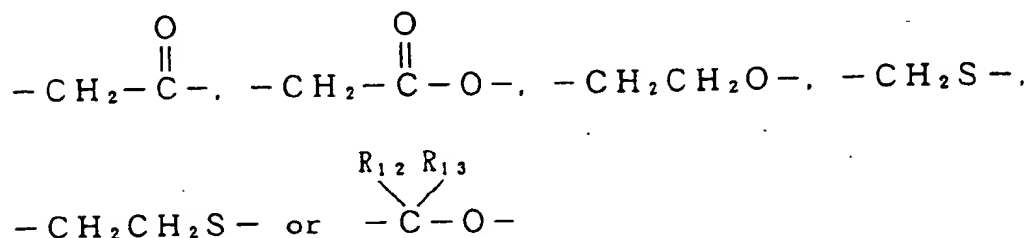
15 wherein  $R_1$  and  $R_2$  are the same or different and are a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkenyl group, a lower alkoxy group, hydroxy group, nitro group, cyano group, amino group, carbamoyl group, an acylamino group, a lower alkylamino group, a lower alkenylamino group or an aralkylamino group, X is an oxygen atom or  $-S(O)_n-$ , wherein n is 0, 1 or 2, A is a bivalent  $C_{1-15}$  hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom, a group of the formula:



25 is an optionally substituted benzene ring,  $B_2$  is  $-(CH_2)_p-$ , wherein p is an integer of 1 to 4, or a group of the formula :



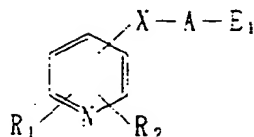
40 wherein  $R_9$  is a hydrogen atom, an optionally substituted lower alkyl, lower alkenyl or aralkyl group, or a group of the formula:



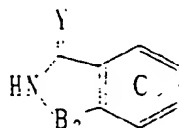
55 wherein  $R_{12}$  and  $R_{13}$  are the same or different and are a hydrogen atom, a lower alkyl group, a lower alkenyl group, a halogeno lower alkyl group, a halogeno lower alkenyl group, an optionally substituted aralkyl group or an aryl group, or  $R_{12}$  and  $R_{13}$  may be linked together to form a ring, or a salt or solvate thereof, which comprises the steps of:

(a) reacting a compound of the formula:



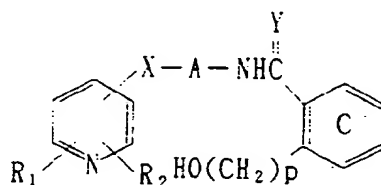


wherein each symbol is as defined above, with a compound of the formula:



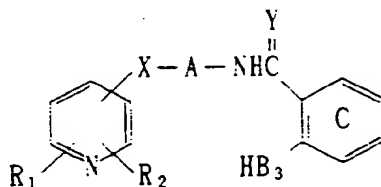
15 wherein each symbol is as defined above; or

(b) when B<sub>2</sub> is -(CH<sub>2</sub>)<sub>p</sub>- wherein p is as defined above, cyclizing a compound of the formula:

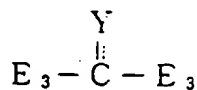


25 wherein each symbol is as defined above, by dehydration; or

(c) when B<sub>2</sub> is -C(=Y)-O-, -C(=Y)-S- or -C(=Y)-N(R<sub>9</sub>)- wherein each symbol is as defined above, reacting a compound of the formula:

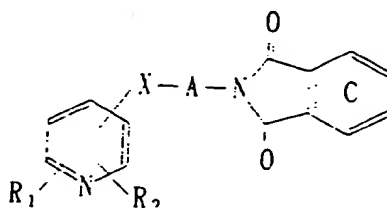


35 wherein each symbol is as defined above, with a compound of the formula:



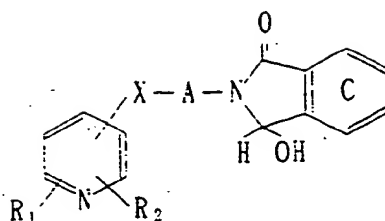
45 wherein each symbol is as defined above; or

(d) when Y is O and B<sub>2</sub> is -C(-OH)H-, reacting a compound of the formula:

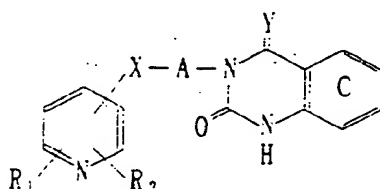


55 wherein each symbol is as defined above, with sodium borohydride, or

(e) when Y is O and B<sub>2</sub> is -CH<sub>2</sub>-, reacting a compound of the formula:



(f) when B<sub>2</sub> is -C(=O)-N(-R<sub>9</sub>)- wherein R<sub>9</sub> is as defined above, reacting a compound of the formula:

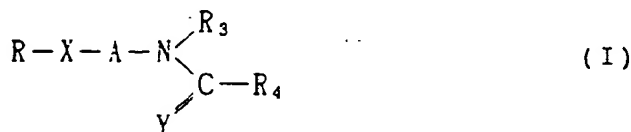


each symbol is as defined above; with a compound of the formula:

 $R_0-E_1$ 

wherein each symbol is as defined above.

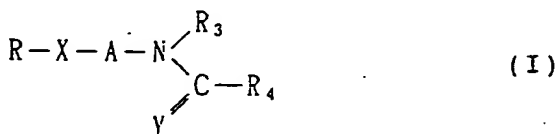
- 25 20. A pharmaceutical composition for providing antiinflammatory, antipyretic, analgesic, antiallergic, immunosuppressing or immunomodulating activity which comprises a pyridine derivative of the formula (I):



wherein R is an optionally substituted pyridine ring, X is a oxygen atom or -S(O)<sub>n</sub>-, wherein n is 0, 1 or 2, A is a bivalent C<sub>1-15</sub> hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom, R<sub>3</sub> is a hydrogen atom or an optionally substituted hydrocarbon residue, R<sub>4</sub> is an optionally substituted hydrocarbon residue or an optionally substituted monocyclic or bicyclic heterocyclic group, R<sub>3</sub> and R<sub>4</sub> may be joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form an optionally substituted heterocyclic group, or R<sub>3</sub> or R<sub>4</sub> may be independently attached to A to form a ring, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or diluent.

21. A pharmaceutical composition according to claim 20, wherein the pyridine derivative is selected from that of the formula (II) as claimed in claim 1;  
that of the formula (III) as claimed in claim 5;  
that of the formula (IV) as claimed in claim 9; and  
that of the formula (V) as claimed in claim 13.

22. A pharmaceutical composition for providing adhesive protein expression inhibitory activity which comprises a pyridine derivative of the formula (I):



wherein R is an optionally substituted pyridine ring, X is a oxygen atom or -S(O)<sub>n</sub>-, wherein n is 0, 1 or 2,

A is a bivalent C<sub>1-15</sub> hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom, R<sub>3</sub> is a hydrogen atom or an optionally substituted hydrocarbon residue, R<sub>4</sub> is an optionally substituted hydrocarbon residue or an optionally substituted monocyclic or bicyclic heterocyclic group. R<sub>3</sub> and R<sub>4</sub> may be joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form an optionally substituted heterocyclic group, or R<sub>3</sub> or R<sub>4</sub> may be independently attached to A to form a ring, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or diluent.

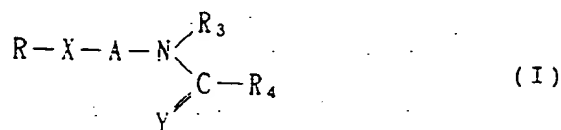
23. A pharmaceutical composition according to claim 22, wherein the pyridine derivative is selected from that of the formula (II) as claimed in claim 1;

that of the formula (III) as claimed in claim 5;

that of the formula (IV) as claimed in claim 9; and

that of the formula (V) as claimed in claim 13.

24. Use of a pyridine derivative of the formula (I):



wherein R is an optionally substituted pyridine ring, X is a oxygen atom or -S(O)<sub>n</sub>-, wherein n is 0, 1 or 2, A is a bivalent C<sub>1-15</sub> hydrocarbon residue whose branched moiety may have a substituent, Y is an oxygen or sulfur atom, R<sub>3</sub> is a hydrogen atom or an optionally substituted hydrocarbon residue, R<sub>4</sub> is an optionally substituted hydrocarbon residue or an optionally substituted monocyclic or bicyclic heterocyclic group, R<sub>3</sub> and R<sub>4</sub> may be joined together with the carbamoyl group or the thiocarbamoyl group to which they are attached to form an optionally substituted heterocyclic group, or R<sub>3</sub> or R<sub>4</sub> may be independently attached to A to form a ring, or a pharmaceutically acceptable salt or solvate thereof, in the production of a pharmaceutical composition for providing antiinflammatory, antipyretic, analgesic, antiallergic, immunosuppressing, immunomodulating or adhesive protein expression inhibitory activity.

25. Use according to claim 24, wherein the pyridine derivative is selected from that of the formula (II) as claimed in claim 1;

that of the formula (III) as claimed in claim 5;

that of the formula (IV) as claimed in claim 9; and

that of the formula (V) as claimed in claim 13.

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